FROM IMMUNOLOGY TO SOCIAL POLICY: EPISTEMOLOGY AND ETHICS IN THE CREATION AND ADMINISTRATION OF PAEDIATRIC VACCINES

BY

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ABSTRACT

This thesis presents an extensive cross-disciplinary exploration of literature appraising epistemological and ethical issues relevant to the current status of paediatric immunisation. It encompasses immunology, epidemiology, medical practice, economics, public health and the formulation and administration of health policy at local, national and international levels. Original insights are drawn from the synthesis of information provided by each of these areas, and future directions are suggested for research and policy formulation.

Recently advanced theories on the function of the immune system are evaluated in relation to trends in vaccine creation. The current state of knowledge regarding neonatal tolerance, immunological memory, and vaccine design is analysed. The complexities of both immunological and epidemiological measurements of vaccine efficacy are outlined, and suggestions are made on improvements to study design and comparability of data.

Ethical issues such as community versus individual rights, the reporting of adverse events, financial incentive schemes, the linking of immunisation with access to other public services such as education and welfare, and the influence of the profit requirements of trans-national corporations are addressed.

The effectiveness of immunisation as a prevention of infectious disease is evaluated in relation to broad-based socio-economic influences on public health. Immunisation is then placed in perspective with other public health measures. The concept of placing immunisation within a broader socio-economic approach to building population health resilience is proposed.

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SECTION ONE: IMMUNOLOGY AND IMMUNISATION

CHAPTER 1

INTRODUCTION

This thesis draws upon an extensive, critical, cross-disciplinary exploration of pertinant literature, identifying and exploring epistemological and ethical issues relevant to the current status of paediatric immunisation. It encompasses immunology, epidemiology, medical practice, economics, public health, and the formulation and administration of health policy at local, national and international levels. It provides a critical review of these areas with the aim of identifying areas of concern in current immunisation policies and practice, and their evidential base. Practical suggestions for improvements in these areas are made, and the implications of current policies and practices are explored in the context of a holistic approach to public health.

The thesis is divided into three sections:

Section 1 **Immunology and Immunisation**
Section 2 **Immunisation and Efficacy**
Section 3 **Immunisation and Social Policy**

1.1 SECTION 1: IMMUNOLOGY AND IMMUNISATION

This section provides a detailed analysis of the epistemology, or state of knowledge, in immunology relevant to the creation and function of vaccines. *Chapter 2: Welcome to Immunology* presents an overview of the current understanding of the operation of the immune system. It demonstrates that many statements about the immune system that are presented as facts in standard textbooks are in fact subject to considerable debate and uncertainty. An analysis is

provided of the relevance of these debates to the creation and function of current and proposed vaccines. In *Chapter 3: Self/Nonself and Danger: A Challenge to the Current Dogma of Immunology* the effectiveness of the traditional view of the immune system as a discriminator between self and foreign molecules is evaluated. In particular it is compared to recently proposed theories that see the fundamental role of the immune system as maintaining the homeostasis of the body and identifying danger in the form of unnatural cell death. The implications of these recent theories for trends in vaccine design are explored.

Chapters 4-6 use this theoretical background as a basis from which to assess the complexities of issues of specific significance for paediatric vaccine design such as the use of *Adjuvants*, current findings on *Neonatal Tolerance*, and the assessment of *Immunological Memory*. The widespread use of adjuvants in vaccine formulation provides support for the danger model of the immune system, as the use of attenuated, inactivated or particulated pathogens (ie, foreign molecules) on their own in vaccines do not provoke sufficient immune response. Adjuvants are required to provide the required danger signal. However, all adjuvants have characteristic problems associated with their use in humans, and these are discussed. The traditional view of neonatal tolerance is re-evaluated in the light of recent experimental and field trial results. In the light of relevant literature, the view that neonates require large doses of antigen is held to be erroneous. It is therefore argued that current vaccine doses be reconsidered. The problems with defining and measuring immunological memory are outlined, as are the implications of those problems for evaluating vaccine efficacy.

1.2 SECTION 2: IMMUNISATION AND EFFICACY

Immunisation and Efficacy looks at the wide range of problems associated with both laboratory based and epidemiological measurements of vaccine efficacy.

Chapter 7: Unintended Longer-Term Consequences of Immunisation reviews areas of public concern in relation to longer-term negative health outcomes, such as atopy and autoimmune disease, as a result of immunisation. It also discusses the potential immunological processes that may underlie these outcomes. *Chapter 8: Measuring Vaccine Efficacy: Immunological Correlates* discusses the inadequacy of using serum antibody levels as a measurement of vaccine efficacy. *Chapter 9: Epidemiological Studies of Vaccine Efficacy* discusses the limitations of epidemiological study designs and suggests simple ways to improve the usefulness of the data collected and make study results more directly comparable. *Chapter 10: Administration of Vaccines: Applying the Remedy* deals with the practical matters involved in supplying vaccines to the public and details areas where poor performance compromises product quality.

1.3 IMMUNISATION AND SOCIAL POLICY

The discussion in this section places immunisation in a broader public health context. It suggests that rather than focusing on a reductionist approach to disease prevention, more comprehensive positive health outcomes might be achieved by formulating policy with the aim of building population health resilience. It presents, in *Chapter 11: Immunisation and Health*, evidence for broad-ranging socio-economic factors as the fundamental cause of diseases, including infectious diseases. This theme is followed through at an international level in *Chapter 12: Health Care, Immunisation and an International Perspective*. Neo-classical economic policies are shown to have had far-reaching negative health outcomes in both developing and industrialised nations. The potential for immunisation to truly reduce the burden of infectious diseases in these circumstances is shown to be limited. Further reasons for this limited effectiveness are raised in *Chapter 13: Administration of Vaccines: Policy and Funding*, which details recent developments and current trends in global immunisation programs, including administrative

procedures, funding issues and the profit making requirements of transnational corporations in relation to the research, development and marketing of traditional and combination vaccines.

A range of epistemological and ethical issues relating to paediatric immunisation are dealt with in *Chapter 14: Epistemology and Ethics*. These include the presentation of scientific knowledge to the public, and procedures which are followed to screen out any aspects of knowledge pertaining to the negative effects of vaccines that the medical fraternity and public health policy makers wish to minimise. This chapter also deals with the ethical issues of informed consent, coercion to immunise, the balance of community versus individual rights, and the utilitarian argument that is so often employed to support these views.

Finally *Chapter 15: The Australian Situation* summarises the current state of paediatric immunisation in Australia. Quality of service, supply and policy is compared with other English speaking industrialised nations. A detailed treatment is provided of the particular circumstances of the indigenous populations.

Chapter 16: Conclusion draws together the diverse threads of this thesis and suggests future directions for research and formulation of public health policy.

SECTION ONE: IMMUNOLOGY AND IMMUNISATION

CHAPTER 2

WELCOME TO IMMUNOLOGY

2.1 INTRODUCTION

The human immune system is a complex system of cellular and chemical interactions. While great developments in our understanding of its workings have been made last century, and especially in the last twenty or thirty years, there are still many areas of mechanism which are poorly understood by immunologists, and theories of function which are actively debated. Some of the reasons for this include technical limitations, problems with interpretation of experimental data, and the complexity of the chemical interactions involved. Investigations have also been limited by the ethical dilemmas associated with *in vivo* experiments on humans, and the uncertainties of extrapolating from findings about the immune systems of

other animals, which are different in many respects (Turner 1994).

This chapter will provide a brief overview of the basic state of knowledge, with particular reference to aspects that are salient to this thesis. This chapter also aims to demonstrate that while general texts on immunology aim to present information in a concise and uncontroversial manner, many areas in immunology are in fact complex and controversial. There are many areas of this discipline where our knowledge is incomplete, and the appreciation of this is constantly evolving. To this end I will offer brief summaries of the basic "facts" as offered by the texts, and follow each of these with a discussion of the complexities of mechanism and theoretical debates associated with each area, with reference to immunisation where appropriate. (For an introduction to immunology see; Abbas, Lichtman & Prober 1994; Alberts et al 1994; Male 1991; Roitt 1991; Roitt, Brostoff & Male 1998; Seymour, Savage & Walsh 1995; Weir & Stewart 1997; Virella 1993).

Recently, some theories which were held as central tenets, such as neonatal tolerance and self/non-self discrimination, have been called into question by new experimental findings. These issues are explored in more detail in Chapters 3 & 4.The ensuing debates have ramifications that concern the formulation and administration of vaccines.

2.2 THE FUNCTION OF THE IMMUNE SYSTEM

The immune system protects the body from potentially lethal infection by bacteria, viruses, fungi and parasites. To do this it employs many different cell types capable of complex direct and indirect chemical interactions. The immune system as a whole has several distinctive features, including memory, tolerance and specificity.

2.3 MAJOR CELL TYPES

The most important cells that are involved in the immune system can be divided

into leukocytes (white blood cells) and antigen presenting cells. (The cells in bold print are most relevant to this thesis):

LEUKOCYTES (white blood cells) include:
- eosinophils
- neutrophils
- basophils and mast cells
- granulocytes
- monocytes
- **lymphocytes** which are subdivided into
  - natural killer cells
  - **T cells**
    - **cytotoxic T cells**
    - **helper T cells**
  - **B cells**

ANTIGEN PRESENTING CELLS
- **macrophages** - found mostly in tissues
- **dendritic cells** - found mostly in lymphoid organs

2.4 ORIGIN AND DEVELOPMENT OF B CELLS AND T CELLS

Cells destined for the immune system start off as immature blood cells with the potential to differentiate into one of several different types (ie. “pluripotent haemopoietic stem cells”). In the foetus these occur in the liver, and in adults they occur in the bone marrow. Pluripotent haemopoietic stem cells differentiate into the many cells that make up blood, including red blood cells, platelets, and white blood cells such as the T and B lymphocytes.

Lymphocyte cells that mature in the bone marrow become B cells, and the ones that migrate to the thymus for development become T cells. Both T and B lymphocytes continually circulate through the blood to peripheral lymphoid organs such as the lymph nodes, spleen, gastrointestinal tract and skin, where they may react with antigens. An antigen is a molecule that provokes an immune response. Some cells in the peripheral lymphoid organs, such as dendritic cells, have the specific function of presenting antigen to T and B cells. They are sometimes referred to as “professional antigen presenting cells” or APC’s.

In their resting, or inactivated state, T cells and B cells are almost indistinguishable in appearance, even with an electron microscope. However, on activation by an antigen they take on very different appearances, and respond in very different ways.

2.5 FUNCTIONS OF B CELLS

B cells make antibodies. Antibodies are proteins (usually called immunoglobulins) which the B cells make in response to a foreign molecule or invading organism. Immunoglobulins customarily act by binding tightly to the pathogenic molecule or cell, thus either inactivating it or marking it for destruction.

B cells deal with harmful invasions of organisms that exist *outside* the body's own cells, such as bacteria. When B cells are exposed to an antigen on the surface of a bacterium, they proliferate to produce more of the appropriate antibody, as well as memory cells that are able to recognise the antigen on future exposure. Their continued functioning depends partly on receiving chemical signals from T cells.

2.5.1 ANTIBODIES

Antibodies are usually immunoglobulin molecules. They serve two quite distinct functions, regulatory and defensive, when they come into contact with antigen. They regulate the activity of the B cell by acting as an antigen receptor and providing the B cell with an activating signal when they come into contact with antigen. They are then secreted into solution to fulfil their defensive role and help destroy the pathogen (Langman & Cohn 1991).

There are several different types of immunoglobulin molecule, most commonly IgA, IgD, IgE, IgG and IgM. IgM molecules are mostly associated with mucosal immunity. IgM and IgD dominate the primary immune response, whereas IgA, IgE and IgG dominate the secondary immune response. IgE molecules are associated

with atopic, or allergic responses. Maternal IgG is passively transferred across the placenta to the foetus *in utero* and maintains a protective role in the infant immune system for some months after birth (Roitt, Brostoff & Male 1998, Ch 23). So far, the aspects of the immune system outlined in Sections 2.4 & 2.5 are almost universally accepted and there is no significant area of controversy relevant to immunisation. However, the following Sections outline areas of immunological theory, which although presented in text books as accepted theory, are actually more complex than they first appear. The details and outcomes of these debates are relevant to a study of immunisation.

2.6 FUNCTIONS OF T CELLS

2.6.1 THE TEXT BOOK VERSION

T cells deal with foreign organisms that invade and cause damage *inside* the body's cells, such as viruses. They secrete cytokines (chemical "cell-movers") which are molecules that affect the functions of other cells.

There are two main types of T cells: cytotoxic and helper T cells. Cytotoxic T cells (also known as killer T cells) are directly involved in defence because they kill infected cells. Helper T cells are indirectly involved in defence because they act to enhance the responses of other cells in the immune system, particularly macrophages (tissue based antigen presenting cells) and B cells.

Helper T cells may be further subdivided into two main categories; T-helper types 1 and 2 (Th1 and Th2). Other subsets such as Th0 and Th3 also exist, but are not as relevant to this thesis.

Th1 cells are responsible for cell-mediated immunity. This is the process whereby they recognise viral antigen on the surface of cells and signal cytotoxic T cells to lyse a virally infected cell. Lysing involves piercing the membrane of a cell so that it

dies. To do this, Th1 cells secrete, amongst other things, the cytokines interleukin-2 (IL-2) and interferon-γ (IFN–γ).

Th2 cells are concerned mainly with humoral immunity. “Humoral” means relating to bodily fluids, rather than cells. This is basically the production of antibodies (immunoglobulins) against harmful extracellular organisms. This involves Th2 cells recognising antigen as presented by antigen presenting cells and producing cytokines such as IL-4, IL-5 and IL-10 that stimulate B cells to make the necessary immunoglobulins.

2.6.2 COMPLEXITIES OF THE ISSUE

This neat classification of T cells over-simplifies a very complex situation (Lucey 1999; Mosmann & Coffman 1989).

> Subpopulations of T lymphocytes can be distinguished using a number of phenotyped or functional criteria . . . For classification by phenotype [the expressed characteristics of an individual], complexities exist in that many markers are not exclusive, and significant overlap occurs between subsets. As well, many markers of interest are expressed on cells other than T lymphocyte subsets. For example, CD4 [Cluster of Differentiation marker, type 4], a marker of ‘helper’ cells, is expressed in monocytes and some dendritic cells . . .The picture is equally complex for classification by function. Within T lymphocyte subpopulations, phenotype and function may not correlate precisely, and both may change dramatically during the cycle of activation, quiescence, and reactivation. Many schemes for classification of T lymphocytes have been proposed, and there are difficulties with each . . . (Seymour, Savage & Walsh 1995, p 65)

In their evaluation of the various schemes of classification, Seymour, Savage & Walsh concluded that the association of the Th1 cytokine profile (Il-2, IFN-γ etc) with cell-mediated immunity, and the association of the Th2 cytokine profile (IL-4, Il-5, IL-10 etc) with humoral immunity was “the most useful” (1995, p 65). However, even this method of classification can lead to various interpretations of experimental results. For example in their discussion of characteristic T cell responses to paediatric pertussis vaccine, Ryan et al argue that;

> Although our conclusion of a mixed Th1/Th2 profile differs from that of a preferential induction of Th1 cells proposed by Zepp et al [1996] the data are not necessarily incompatible. Zepp et al used IL-10 as an index of Th2 cells and did not measure IL-5 or other Th2 cytokines. However, IL-10 is not produced by all Th2 clones and its secretion is not confined to Th2 cells, or even to T cells, because macrophages are also important producers of this cytokine. (Ryan et al 1998, p 9)

After discussing the complexities of various T cells' responses in relation to childrens' immunisation with different pertussis (whooping cough) vaccines, Ryan and colleagues observe that:

> The dogma that Th1 and Th2 cells are associated with cell-mediated and humoral immunity, respectively, has recently been reevaluated. . . It appears that the mechanism of protection involves a complex combination of antibody and T-cell responses . . . (Ryan et al 1998, p 9)

For immunisation this implies that antibody-count, the accepted standard measure of vaccine effectiveness, is an inadequate measure. Different antibodies (Ig A, IgG, Ig M etc) are produced at different stages of the immune response, so in research studies it needs to be clarified which antibody or antibodies are being measured. Further to this, antibody-count focuses on only a small part of the total immune response, and a part that, on its own, is insufficient to fully provide immunity. Ryan and colleagues caution that:

> . . . evaluation of cell-mediated immunity has been largely overlooked in the study design of most of the vaccine efficacy trials. (1998, p 9)

This may provide one explanation for observation that "antibody titres . . . do not correlate with vaccine efficacy" (Granoff & Rappuoli 1997). This has been a problem with all the standard childhood vaccines: measles (Aaby et al 1987; Aaby et al 1990; Burstrom, Aaby & Mutie 1993; Kenya 1990; Samb et al 1995), pertussis (Edwards 1993; Giuliano et al 1998; Ryan et al 1998; Olin 1995), polio (Faden 1993) and Hib (Granoff et al 1993).

2.7 MAJOR HISTOCOMPATABILITY COMPLEX

2.7.1 THE TEXT BOOK VERSION

T cells recognise antigen in the form of peptide fragments. Peptides are molecules containing two or more amino-acids linked together. As foreign proteins degrade, or are broken down inside the cells they have infected, they release peptide fragments. Special proteins inside the cells bind these peptides and carry them to the cell surface where they are presented to the T cells. These special proteins are called MHC molecules because they are encoded by a group of genes called the major histocompatability complex (histo=tissue).

There are two classes of MHC molecules. MHC class I molecules are constituent parts of nearly all nucleated cells. Their function is to present foreign peptides to cytotoxic T cells. MHC class II molecules are found only on part of the specialised cells of the immune system, such as B cells, macrophages and other antigen presenting cells. These are cells that are involved in humoral immunity, that is, able to take up foreign antigens from the extracellular fluid. They present foreign peptides to helper T cells.

The genes that code for MHC molecules are amongst the most polymorphic in higher vertebrates. There are five or more genes which encode for MHC molecules and for each gene there may be as many as 100 different alleles (alternative forms of a gene). Each allele gives rise to a different version of the protein, so it is rare for two individuals to have identical MHC proteins. This is why it is difficult to match donors and recipients for organ transplantation, and why graft rejections are such an issue in transplantation biology.

2.7.2 COMPLEXITIES OF THE ISSUE

An individual's MHC profile influences various aspects of their immune response.

The full extent of these influences and the implication of this for vaccine design have only recently become the focus of research.

Studies have shown that responses to particular vaccines, varying from non-response to hyper-response, can be linked with characteristic MHC profiles. This has been documented in relation to various hepatitis B vaccines, where it has been shown that non-response to hepatitis B surface antigen, which occurs in up to 10% of the population (Hohler et al 1998), is associated with expression of particular alleles at certain MHC genes (Caillat-Zucman et al 1998; Hohler et al 1998; McDermott et al 1997; Mineta et al 1996). One study on neonates suggests that the MHC profile associated with non-response to hepatitis B surface antigen vaccine exhibits some alleles that are classically associated with autoimmune disease (Martinetti et al 1995).

A similar pattern has been shown for responses to measles vaccination. However, the gene loci and alleles involved are different to those apparently involved in the hepatitis B vaccine response (Hayney et al 1998).

There are also MHC profiles associated with various ethnic groups, and these too have a bearing on characteristic vaccine responses (Hsu et al 1993; Worku et al 1997). This factor is part of the observed broader ethnic variations in general immune system characteristics. These include differences in the proportion of types of T cells and other serum components, and may be caused by a combination of genetic and environmental factors. The environmental factors may include characteristic patterns and levels of exposure to pathogens, and nutrition. An understanding of the

> . . . potential influence of such immune adaptation on the response to vaccination or pharmaceutical therapy may be important in the development of new strategies of medical intervention in different geographical regions or ethnic groups. (Worku 1997)

The MHC profile is an important source of variation in characteristic immune responses, but not the only one. The existence of different ethnic and geographic profiles can be clearly defined while still encompassing a broad range of individual responses within that profile. This is an important factor to be kept in mind for both vaccine design and epidemiological studies of vaccine safety and efficacy.

2.8 MEMORY

2.8.1 THE TEXT BOOK VERSION

"Memory" refers to the immune system's ability to mount a faster response on re-exposure to a pathogen. On first exposure to an antigen it takes several days to produce a protective level of antibodies. This is the primary response. On subsequent exposure to the same antigen, a much higher level of antibody production, or secondary response, can be reached in only two or three days. This is one of the foundations of the practice of immunisation.

The theoretical basis of immunisation is that the primary exposure to a pathogen comes from a controlled dose of vaccine. This usually consists of a killed or attenuated (weakened) version of the pathogen, or more recently of a part of the pathogen such as a section of a bacterial capsule, some viral DNA, or protein fragments (peptides) which are characteristic of the pathogen (Gellin 1998). These are designed to provoke an antibody response without inducing the disease. On secondary exposure to the wild pathogen the body should then be able to mount a fast and effective secondary response.

2.8.2 COMPLEXITIES OF THE ISSUE

The mechanism of immunological memory is subject to debate (Matzinger 1994, Mitchison 1992). The traditional view is that:

> . . . newly made B and T lymphocytes of the immune system are short-lived, dying within a few weeks to make room for new cells. . . [and] if they see an antigen, they divide to make armies of effector cells to combat the infection and of long-lived memory cells which can remain quiescent for years. (Matzinger 1994)

However, with new experimental evidence relating to the lifespan of various cells of the immune system (Hou 1994; Lau et al 1994; Müllbacher 1994), this theory has been questioned.

The view proposed by Gray and colleagues (Gray & Skarvall 1988, Gray & Matzinger 1991) is that:

> . . . memory cells are not intrinsically longer-lived than virgin cells but that memory depends instead on the persistence of antigen. (Matzinger 1994)

The immune system needs both short and long-term memory capability. Short-term memory caters for pathogens that are common in the environment, and to which exposure is relatively frequent, for example the currently circulating strains of influenza virus. Long-term memory is required for pathogens to which exposure is infrequent, but may have serious consequences, for example *Clostridium tetani*, the bacteria that causes tetanus.

Short-term memory appears to be the province of follicular dendritic cells, which bind antigens and then release them slowly, for capture by B cells which present them to memory T cells. This response continues for months, maintaining a constant state of ready immunity. Any subsequent infections are quickly responded to, and boost the store of retained antigen (Matzinger 1994). This has been supported by experimental findings that show that if murine (mouse) memory cells are transferred into new recipients without corresponding antigen, they will lose their memory function after a few weeks. Memory persists if antigen is given at the time of transfer (Gray & Skarvall 1988; Gray & Matzinger 1991).

The mechanism of long-term memory is not as clearly understood. Matzinger favours a model of cross-reactivity. Antibodies to one pathogen have some capacity to respond to others, for example with

> . . . the B-cell response to flu, where antibodies to a new variant are overwhelmingly directed to antigens shared with a previously seen variant. Because T cells see short peptides of 8-13 amino acids they can cross-react to variants of the original peptide as well as to unrelated MHC/peptide complexes. (Matzinger 1994)

T cells are also able to respond to antigens presented on B cells, and B cells are efficient at capturing low-density antigens. This means that:

> As an individual ages, because of the two features of cross-reactivity and response to B cells, the system will become dominated by memory cells that also respond to current environmental antigens. In this way the immune system can maintain memory to very old and rare pathogens while responding to new ones. (Matzinger 1994)

Mitchison, however, views immunological memory very differently. He believes that "there are no markers of memory, but only markers of activation" (1992, p 5).

His view of the mechanics of memory is as follows:

> . . . regulatory T cells become activated, acquire [chemical, surface] markers . . . proliferate, and become hyperreactive to antigen (the detailed kinetics of these four processes have still to be worked out). After a more or less brief phase of this sort, the stimulated cells revert to a resting phase and lose the markers, but remain present in expanded number. Thus, memory in the Th compartment has two components, one of hyperreactivity and the other of expanded cell number. (Mitchison 1992, p 5)

This is functionally nearer the traditional model than Matzinger, although conceptually more distant because it focuses on "activation" rather than "memory". However, it still "raises the question of which of the components mediates protective immunity against infection in humans" (Mitchison 1992, p 5).

It is important that these issues continue to be critically examined, because both the theory and mechanics of immunological memory are core concerns in the design of effective vaccines. The current trend in vaccine design away from whole attenuated or killed pathogens in favour of fragments such as peptides, surface markers and DNA makes a thorough understanding of this area even more vital.

2.9 SPECIFICITY

2.9.1 THE TEXT BOOK VERSION

Separate vaccines are required for each pathogen because immune responses are specific; immunity to one pathogen does not readily transfer to another one, even if it is similar (although there do exist some elements of cross-reactivity that are not clearly understood (Matzinger 1994)). The immune system is able to distinguish differences as small as one amino acid in two otherwise identical proteins consisting of hundreds of amino acids (Alberts et al 1994). This is why problems exist in creating a vaccine for mutable pathogens such as influenza viruses, because they make constant small changes (antigenic drift) with the occasional major change (antigenic shift) in surface proteins. A new influenza vaccine must be made each year with the scientists' best guess as to that year's prevailing strains (Gellin 1998). It is also the reason why the polio vaccine covers three types of polio virus (NHMRC 1997, p 97), and the pneumoccocal vaccine covers twenty-three strains of bacteria (Örtqvist et al 1998).

2.9.2 COMPLEXITIES OF THE ISSUE

This specificity is combined with a broad range of possible responses, making the rational design of vaccines a complex task, especially as antibody count, although still the accepted measure of a successful response, has proven inadequate. Manufacturing processes may alter the immunogenic properties of the vaccine components, for example the use of formaldehyde to inactivate bacteria or their toxins, often alters the chemical structure of the antigenic epitopes, which act as

binding sites for B and T cells. This makes it difficult to assess the immunogenicity of manufactured antigens in relation to their wild-type counterparts (De Magistris et al 1995).

2.9.3 PERTUSSIS VACCINES

The traditional view of a clear dichotomy of humoral immunity for extracellular pathogens (eg bacteria) and cell-mediated immunity for intracellular pathogens (eg viruses) is increasingly being called into question. For example with pertussis vaccine

> . . . evidence is emerging that humoral immunity alone may not be sufficient to confer protection . . . It is now accepted that *B. pertussis* is not exclusively an extracellular pathogen, but that it has the ability to invade and survive within mammalian cells . . . suggesting that cell-mediated immunity may [also] be required. (Ryan et al 1998, p 1)

Murine studies have shown that transfer of T cells from immune mice can confer immunity in the absence of a detectable antibody response (Mills et al 1993).

Whole cell pertussis vaccines are manufactured by similar methods in many countries, but "the vaccines frequently elicit markedly different immune responses" (Cherry 1996, p S260) and "postvaccination serologic correlates of protection have not been established" (Guiliano et al 1998, p 983). That is, the required amount of antibody or other protective mechanisms present in the serum component of blood is, as yet, unknown. Production of interferon-γ appears to be involved, but antibody titres decline rapidly after vaccination. Levels of antibody are

> . . . poor 1 month after the third dose [of vaccine], and no antibody was detected in nearly all children 15 months after whole-cell vaccination. (Guiliano et al 1998)

However "T-cell responses [can] persist for at least 4 years after immunization with a whole-cell vaccine", but not in all children (Ryan et al 1998, p 3).

There is some debate over whether whole-cell pertussis vaccines induce a predominately Th1 or Th2 cytokine profile. The immune system should ideally mount a Th1 response, however, other factors such as general health of recipient, concurrent infections, number of vaccines administered at the same time, predisposition to atopy and exposure to environmental toxins may be causative factors in shifting towards a predominately Th2 profile (Ferry & Wessely 1997; Rook & Zumla 1997; Aaby 1995).

The human immune system responds very differently to the whole cell and acellular vaccines, making an assessment of the relative efficacy of different vaccines a difficult task. The responses to acellular vaccines vary widely in relation to the number and type of *B. pertussis* antigens included (detoxified pertussis toxin, filamentous haemoglutinin, pertactin and fimbriae are the most common components (Ryan et al 1998)). T cell responses to various acellular vaccines have ranged from predominately Th1, Th2 or Th0 to mixed Th1/Th2, Th2/Th0 (Ryan et al 1998).

The difficulties of attempting to correlate observed immune response with vaccine efficacy is further complicated by the reported fact that:

> [The] case definition of pertussis . . . developed by the World Health Organisation for use in vaccine efficacy trials . . . eliminates some laboratory-confirmed cases from efficacy calculations. Because these cases are more common in vaccinees than in controls, vaccine efficacy appears better than it truly is whereas less effective vaccines seem comparable with their more effective counterparts. (Cherry 1997)

2.9.4 HIB CONJUGATE VACCINES

The situation is similar with the more recently developed Hib vaccines. All the Hib vaccines currently licensed differ chemically and structurally, and possess different

immunogenic properties.

> Different Hib conjugate vaccines elicit specific antibody responses by different immunologic mechanisms. However, it is uncertain whether these immunologic differences relate to the ability to these vaccines to prime infants for memory antibody responses to unconjugated PRP [polyribosylribitol phosphate, the polysaccharide capsule of *Haemophilus influenzae* Type B]. Previous studies investigating priming by conjugate vaccines have not addressed this question directly . . . (Granoff et al 1993, p 663)

The study by Granoff et al argues for the need to:

> . . . determine the structural basis for these immunologic differences, since such information may be helpful in more rational [vaccine] design. (1993, p 670)

and also to determine the clinical consequences of the differences in immune response.

2.9.5 MEASLES VACCINES

There are frequent reports of outbreaks of measles in highly vaccinated populations (for a selection of reports see: Burstrom, Aaby & Mutie 1993; Christopher et al 1983; Cohn et al 1994; Grimes & Woolbert 1989; Herceg, Passaris & Mead 1994; Yeager et al 1977), although there is some indication that cases may be milder in previously vaccinated individuals (Aaby et al 1986). As with other vaccines it has been shown that antibody count does not correlate with ability to respond to measles antigen (Linnemann et al 1982) and up to 10% of vaccine recipients are seronegative, that is they show an antibody count of less than 10 IU/L even after re-immunisation (Cohn et al 1994).

However, measles vaccine differs from other paediatric vaccines in that the key benefits of the vaccine lie not only in its specificity in providing protection from that particular disease, but from the broader health gains to be had from a generalised,

non-specific stimulation of the immune system (Aaby 1995; Aaby et al 1995).

Measles virus is associated with general immunosuppression. It suppresses the functions of both B and T lymphocytes, and reduces production of IgG (Tishon et al 1996), however, far from having negative consequences, this means that the virus acts as a general stimulant to the immune system. Recovery from this broad suppression has the long-term result of increasing protection against other non-related infections (Aaby et al 1995). The live, attenuated measles vaccine plays an important role here because it provides the same beneficial stimulatory effect as the disease, but lacks the intensity of infection and associated potential dangers. Especially in developing countries this

> . . . protection against measles could reduce total mortality [by] more than the share of deaths attributed to acute measles. (Aaby 1995, p 674)

It is therefore important that there exists a clear understanding of the immune response to a particular pathogen, so that vaccines can be designed which provoke a response as near to the natural one as possible. It is also important to keep a broad awareness of the long-term function of the immune system as a whole (see discussion of the work of Cohen and Coutinho in Chapter 3), and that administered vaccines may have consequences that reach beyond their specific purpose.

2.10 TOLERANCE

2.10.1 THE TEXT BOOK VERSION

Tolerance is the ability of the immune system to mount attacks against foreign invaders while leaving similar tissue of its own organism unharmed. This is often discussed under the heading “self/non-self discrimination”. There has been much interest in clarifying how the immune system does this, and recent experimental findings have lead to a review of the traditional model. The issue will be discussed in detail in Chapter 3)

2.10.2 COMPLEXITIES OF THE ISSUE

For immunisation to work effectively it is essential that the immune system "remembers" its exposure to the pathogen.

Until recently it was held that tolerance developed during a "window" of foetal and neonatal life, before the body is exposed to the daily barrage of foreign antigens. During this time, in the thymus, any developing lymphocytes that are self-reactive are eliminated. There were various explanations of the mechanisms involved, but little dispute of the theory (Ridge, Fuchs & Matzinger 1996). Now, however, as a result of experimental findings reported in *Science* (Forsthuber, Yip & Lehmann 1996; Ridge, Fuchs & Matzinger 1996; Sarzotti, Robbins & Hoffman 1996), the theory is being questioned. This has repercussions for neonatal and infant vaccines and will be discussed in Chapter 5.

2.11 CONCLUSION – IMPLICATIONS FOR PAEDIATRIC VACCINES

The workings of the human immune system are complex, and there is much that remains to be understood. The design of early vaccines centred around the killing or weakening of wild pathogens to provide a safer stimulus, but one which would still, ideally, closely mimic the individual's "natural" immune response. This operated fairly successfully without a deep understanding of the mechanics involved (Cutts & Smith 1994). The smallpox vaccine that was successful in eradicating that disease and many of the current paediatric vaccines, for example polio and measles, are of this type.

Safety, however, is an important issue:

> It is likely that some of the vaccines which have been in use for many years would now, as newly developed candidate vaccines, have difficulty in passing the regulatory authorities on the grounds of safety. (Ada 1994b, p 67)

This is because the inactivation process may be incomplete, or attenuated pathogens may revert to their original virulence. This has been documented particularly in relation to both the inactivated (Salk) and live (Sabin) polio vaccines (Faden 1993; Smith 1990).

The current approach to vaccine design places emphasis on the use of fragments of pathogens, for example peptides, surface molecules and segments of DNA, on the assumption that this is safer than using a whole pathogen. To do this successfully, however, needs a much greater understanding of the mechanics involved, and the detailed characteristics of an appropriate protective immune response.

Further to this, it also requires an awareness of the broader implications that these immune reactions may have within the network of the immune system as a whole. There is also a need to be mindful of the way that the immune system interacts with other biological systems within the body such as the nervous system. These broader issues have been highlighted in recent debates on the function of the immune system, and will be discussed in detail in Chapter 3.

As this chapter has shown, immunology is a complex and evolving discipline, and there are few easy answers to even apparently simple questions. The rational design of safe and effective vaccines is a considerable challenge requiring researchers to stay at the forefront of advances in both mechanism and theory. Recently there have been significant challenges to traditionally held beliefs in areas including the function of the immune system as a whole, the characteristics and development of infant immune systems (with particular reference to neonatal tolerance) and the development and role of adjuvants in vaccines. The following chapters will examine these issues in detail with particular reference to the safety, efficacy and administration of paediatric vaccines.

CHAPTER 3

SELF/NON-SELF AND DANGER: A CHALLENGE TO THE CURRENT DOGMA OF IMMUNOLOGY

3.1 INTRODUCTION

For the last fifty years immunology has been dominated by the view that the central function of the immune system is to discriminate self from non-self. If an antigen is determined to be non-self the immune system then mounts an appropriate response to protect the body from invasion. This perspective has guided theorising, and the design and interpretation of experiments, ever since Burnet & Fenner put forward the self-marker hypothesis in their 1949 publication *Production of Antibodies* (Silverstein 1989; Tauber 1998). It is still the dominant view, and has some strong defenders (see for example, Cohn 1992; Cohn 1998; Janeway,

Goodnow & Medzhitov 1996; Langman 1989; Langman & Cohn 1996b; Langman & Cohn 1997; Mitchison 1993; Silverstein 1996; Silverstein & Rose 1997).

Until recently the only significant alternative was Jerne's idiotypic network theory (Jerne 1974), and various derivations of this, such as those by Cohen and Coutinho (Cohn 1989b, pp 35-37; Coutinho & Bandeira 1997; Tauber 1998, pp 465-468). Although there has always been wide acknowledgement of serious flaws in the self/non-self model (Matzinger 1994; Cohn 1989a), most immunologists have put their energy into trying to preserve the model by finding a way around these, rather than seeking to evolve a new model (Matzinger 1994, pp 993-995).

In the last ten years, however, viable alternative perspectives have been proposed and there has been a serious renewal of debate. The most significant of these is Matzinger's danger model (Matzinger 1994) supported by the experimental results reported in three papers published in *Science* (Forsthuber, Yip & Lehmann 1996; Ridge, Fuchs & Matzinger 1996; Sarzotti, Robbins & Hoffman 1996) which have challenged accepted thinking on neonatal tolerance.

Other models such as stranger (Janeway, Goodnow & Medzhitov 1996) and integrity (Dembic 1996) have arisen during the ensuing discussion. These reflect the conceptual shift that has been made in interpreting the primary function of the immune system. Recent theories have moved away from seeing it as an isolated system that discriminates between self and non-self, and towards viewing it as a system that works in conjunction with other body systems, such as the nervous system, to preserve homeostasis.

There is still considerable debate over whether or not Matzinger's danger model has actually "overthrown" the traditional self/non-self model (Janeway, Goodnow &

Medzhitov 1996; Lafferty & Gazda 1997; Langman & Cohn 1997; Silverstein 1996; Silverstein & Rose 1997; Tauber 1998). The debate may result in a change in prevailing dogma, or it may simply bring a richer perspective to the current one, but however it resolves, the issues raised by Matzinger and her supporters have implications for the theoretical basis of the practice of immunisation.

3.2 SELF/NON-SELF DISCRIMINATION

3.2.1 HISTORY

The self/non-self discrimination model carries the imprimatur of several decades of general acceptance. It is central to "Classical Immunology" (Lafferty and Gazda 1997) and is presented as dogma in widely prescribed immunology textbooks (Abbas, Lichtman & Pober 1994; Alberts et al 1994; Male 1991; Roitt, Brostoff & Male 1998; Weir & Stewart 1997). Many experiments apparently support it (as reported in Silverstein 1989; Silverstein & Rose 1997) and until recently it has managed to incorporate most new experimental findings. Supporters such as Silverstein (1996) and Langman & Cohn (1996b) argue it also copes with the apparently discordant findings on neonatal tolerance recently reported in *Science* (Forsthuber, Yip & Lehmann 1996; Ridge, Fuchs & Matzinger 1996; Sarzotti, Robbins & Hoffman 1996 - these will be discussed in detail in Chapter 5). They hold that recent theories such as Matzinger's danger model and Dembic's integrity model do not pose a significant threat, and are in fact little more than elaborations of mechanism (Langman & Cohn 1996b).

The prevailing view that the immune system's primary function is to discriminate between self and non-self, and then to mount an appropriate response to non-self, has its roots as far back as Metchnikoff (1892, 1901). He was impressed by the way cells could identify and encapsulate dangerous material. This was followed early this century with the demonstration of antigen-antibody specificity. The developing discipline of immunology was faced with the task of explaining the

specificity of immune responses, and the mechanisms that provoke their production (Silverstein 1989).

Burnet began with a self-marker hypothesis (Burnet & Fenner 1949) postulating that cells in the body have a molecule (or molecules) on their surface that acts as an indicator of self. Cells of the immune system recognise this and leave those cells alone; they tolerate them. This was confirmed and elaborated on with the discovery of the MHC molecule.

Burnet later developed the clonal selection theory, which attempts to explain the origins of self-tolerance (Burnet 1959). The clonal selection theory holds that while T cells develop in the thymus of the foetus and neonate, any self-reactive T cell clones are eliminated before they have been exposed to foreign antigens. The only ones that survive are those which are able to react to foreign antigens, but which do not react to cells that carry a “self” marker. The immune system thereby “learns” not to react to self cells.

Burnet’s theory held that the ability to make the self/nonself discrimination was acquired early in the life of the individual, and did not adequately explain how it was maintained throughout life. Lederberg (1959) attempted to address this problem by postulating that the ability to make the self/nonself discrimination is learned early in the life of the relevant cells, and that this learning process occurs throughout the life of the individual.

Lederberg suggested that cells are born tolerizable (able to be rendered unresponsive to a specific antigen) only, and that an encounter with antigen leads to inactivation. After a time without encountering antigen, a young T cell enters an inducible state whereby encounter with antigen stimulates the cell to develop an effector (defence) function. Lederberg postulated that self is present when antigen

responsive T cells are born and it persists, whereas nonself appears after development and is transient (partly because these T cells eliminate it!). However,

> His theory turned out to be wrong, and for a priori reasons; there would be no way to control the mutants of anti-nonself cells to anti-self cells, a lethal situation . . . Nevertheless, it was a giant step forward, and subsequently it became incorporated into a larger context . . . (Cohn 1994, p 24)

That is, it formed the basis of Bretscher and Cohn's (1970) associative recognition theory, which will be discussed later.

Various experimental findings have supported the development of the theory of self-nonself discrimination (Stockinger 1996), including the famous one by Owen that showed that dizygotic (non-identical) twin calves exposed to each other's blood *in utero* are later tolerant of their twin's erythrocytes (Owen 1945). From this came the widely accepted notion of a "window" of neonatal tolerance, or a time just after birth when the immune system has not yet developed its ability to respond to antigens as a mature system would. During this period exposure to antigens apparently produces no response. Tolerance of antigens can persist for some time, and this has made the formulation of neonatal vaccines an uncertain and complex endeavour, and has led to a general belief that it is necessary to use very large doses of antigen to provoke an antibody response from an immature immune system (Sarzotti in Pennisi 1996; Stockinger 1996).

The current version of self/nonself discrimination (as found in standard texts such as Abbas, Lichtman & Pober 1994; Alberts et al 1994; Male 1991; Roitt, Brostoff & Male 1998; Weir & Stewart 1997) maintains the original assertion that tolerance to self occurs during a discrete period of foetal and neonatal development, and that the immune system uses molecular markers expressed on cell surfaces to identify self components. However, the details of mechanism have proven to be highly complex and open to interpretation. For example, there is dispute over how self-

reactive clones are dealt with in the thymus; whether they are deleted (killed) or made anergic (inactive), and if so, how this is accomplished. On the matter of identifying molecular markers, there is general support for Bretscher & Cohn's (1970) associative antigen recognition model, which holds that two different molecular signals (epitopes) on an antigen must be recognised simultaneously to activate lymphocytes, but there are various developments of this, such as that by Lafferty & Cunningham (1975) who brought in the role of co-stimulation from antigen-presenting cells. Others such as Matzinger (1994), and Dembic (1996) postulate a third signal. And there is also debate over the exact nature of chemical signalling and interaction between B cells, the various types of T cells, and antigen presenting cells.

With so many areas where the details of mechanism are under dispute there is fertile ground for the development of new theories.

3.2.2 PROBLEMS WITH THE THEORY OF SELF/NONSELF DISCRIMINATION

3.2.2.1 "Self"

Perhaps one of the greatest weaknesses of the theory of self/nonself discrimination is evident in its name, for there has never been any clarity or agreement on the definition of "self"! This is not only the case in immunology, but also in the disciplines of philosophy and bioethics where considerable time has been spent debating a formal definition of what is meant by the vernacular usage. The first formal mention of the term "self" in relation to the immune system is generally attributed to Macfarlane Burnet in his early treatise on the clonal collection theory (1959). Here Burnet placed it in quotation marks and used it as a metaphor for "host" or "subject". He was quite aware that "*Self* is not a technical term . . . it was used hesitantly. And with good reason." (Tauber 1994, p 132). Nevertheless, the undefined term that started off as a metaphor gradually found its way into highly technical scientific debate.

As Matzinger observed in 1994, after nearly fifty years of the development of the self/nonself theory, immunologists are still unable to agree on a definition of either self or nonself. Some suggestions for self have included (list compiled from Matzinger 1994, p 993, unless otherwise stated):

General definitions of self:

a) Everything encoded by the genome.
b) Everything under the skin, including structures encoded by commensal [harmless] genomes.
c) Tissue accessible to lymphocytes, ie. a) or b), but excluding "privileged" sites such as brain, cornea and testes.
d) The set of bodily proteins that exist at a concentration above a certain threshold.
e) Molecules participating in the idiotype/anti-idiotype network. (See Section 3.3.1 on Jerne's idiotypic network theory.)

Self for T cells:

f) The set of peptides found complexed with MHC molecules.
g) Antigen presenting cells and thymic epithelium only.

Self for B cells:

h) Cell surface and soluble molecules.

Self for the immune system:

i) When applied to the immune system the terms self and nonself remain heuristic (from Langman & Cohn 1996a, p 544).
j) It is the immune system, not dictionaries or immunologists, that defines "self" (from Cohn 1998, p 481).

A dictionary definition of "self" is:

> . . . a person's or thing's own individuality or essence, person or thing as object of introspection or reflexive action. (Sykes 1976)

It is interesting that these immunological definitions range from something that most people would be able to see as relevant to the vernacular usage (a or b) down to a particular set of molecules or cell types (f to h) and then to something that is not a definition at all (i and j). After fifty years of debate immunologists have not just remained undecided about their definition of self, they have also been unable to decide at what level of specificity they should make the definition.

Tauber suggests that with

> . . . so much dispute surrounding the definition of self . . . the "self" might be better regarded as only a metaphor for the immune system's silence, i.e., its non-reactivity, which in itself is problematic, since this silence might be actively attained through tolerance mechanisms . . . (1998, p 468).

Actively tolerant to what? And how? Self still founders on a lack of definition.

The definition of nonself is equally unclear because there are actually very few things to which the immune system will mount an attack. "Foreign" items to which the immune system does not normally respond include: silicone, bone fragments, solitary haptens (single epitope molecules), many peptides, food and commensal microorganisms. In fact

> . . . very few antigens are particularly immunogenic; . . . the immune system focuses on certain subsets of foreign antigens that carry "markers" of foreign-ness, like those of bacterial cell walls that act as adjuvants. (Janeway in Matzinger 1994, p 994)

As well as the above mentioned non-self items which do not provoke a response, there are some aspects of self to which the immune system does not normally respond, but can do so in certain circumstances. This category includes such diverse substances and processes as: myelin basic protein, acetylcholine receptor (Matzinger 1994, p 994), the constant basic housekeeping task of removing toxins and dead cellular matter, as well as autoimmune responses that occur regularly during inflammation (Nakamura & Nakamura 1992), and the more dramatic cases of autoimmune disease. As Matzinger points out, the immune system "doesn't really discriminate self from non-self, but *some* self from *some* non-self" (1994, p 994), and this complicates the question of discrimination. What is the immune system actually discriminating for, and how is it doing it? This is where Matzinger brings in her danger model. How she does this will be discussed later.

As for the term “self”, other expressions have been proposed, such as “chemical individuality” or “biological ego”, but they apparently lack “the rich evocation of *self*” (Tauber 1994, p 132) and have not caught on. So ironically, in the detailed debates of one of the most technical areas of biological science, this vague term, with all its inherent problems, remains in use.

3.2.2.2 Associative Recognition

A major concern with the clonal selection theory is the concept of having a discrete period during development during which the immune system “learns” to identify and tolerate self components by deletion of self-reactive clones. This brings with it the problem that:

> If the generation of diversity in the immune system results from a random mutational process there must be a mechanism that allows self/not-self discrimination to occur, not only during the neonatal period, but throughout the lifetime of the individual. (Lafferty and Gazda 1997)

This prompted the two signal model of Bretscher and Cohn (1970) which brought in the notion of associative recognition of antigen, whereby two different molecular signals (epitopes) on an antigen must be recognised simultaneously to stimulate lymphocytes into antibody production. Cohn has argued that associative antigen recognition is an obligatory part of the self/non-self discrimination model because:

> Any physiological function mediated by a destructive effector activity must have a mechanism for making a self/nonself discrimination that operates at the recognitive level. (1992, p 323)

The associative antigen recognition model works to preserve self components from attack by the immune system in the following way: *two* signals are required for lymphocyte activation. The *first* signal alone is tolerogenic, that is it inactivates (or deletes) the lymphocyte. Any self-reactive cells that arise by random mutation will

receive only the first signal and become inactivated. Simultaneous exposure to the second signal is required for activation. The *second* signal is supplied by T helper cells in response to exposure to antigen and is called “help” (although Cohn personally favoured the term “cooperation” (Cohn 1989a, p xxi)). This model allows for self/nonself discrimination by the immune system because self (signal one only) produces no response, whereas nonself (signal one plus signal two) activates an immune response. However it fails to account for how the T helper cells recognise foreign antigen, and returns us to the question “how does the immune system discriminate?”

Cohn attempts to deal with this issue but although he outlines a complex series of signalling pathways involving antigen presenting cells and interleukins, he finally gets to:

> . . . where does the initial antibody anti-Nonself, required to arm APC [antigen presenting cells] come from? . . . My best guess is that priming is the functional role of IgD [immunoglobulin D molecules]. (Cohn 1989b, p 30)

And this still does not explain what criteria are used by the IgD molecules to distinguish nonself antigens!

There is also the sheer number of different self components to which a lymphocyte needs to be tolerant, and the fact that it cannot possibly be exposed to all of them during its development in the thymus. This is why Lederberg suggested a period of time during the development of each cell when it was tolerisable only, to allow for circulation out to the peripheral lymphoid system where it contacts a greater range of self components. It is also another reason why Bretscher and Cohn (1970) brought in the associative recognition of antigen. It is clearly explained by Langman (1989) that the effect of associative recognition is that the immune system defaults into an OFF setting, requiring a second signal to be turned ON. However, this

attempt to explain how a lymphocyte can be tolerant of self components that it has never encountered before still founders on the problem of explaining how it then distinguishes a nonself component that it has never encountered before either! Cohn here resorts to self being persistent and nonself being transient (Langman & Cohn 1996b), but this does not solve the problem.

The Lafferty & Cunningham (1975) model, which also postulates two signals, is different in a couple of significant respects. Firstly their signal one, rather than inactivating the lymphocyte, is simply not enough to activate it. Their second signal comes not from a T helper cell, but rather from presentation of an MHC-peptide complex on an antigen presenting cell, and is called co-stimulation. This model better fits the available empirical data, but once again runs into the discrimination issue because they acknowledge that antigen presenting cells are unable to make a self/nonself discrimination. They, however, acknowledged that:

> . . . by following this path we are forced to seriously consider abandoning the self/not-self metaphor for the immune system . . . (Lafferty & Gazda 1997, p 121)

They favour Matzinger's danger model because:

> The danger metaphor for the immune system moves us away from theories of self/not-self discrimination. Once we take this step there is no need, from a purely theoretical viewpoint, for the involvement of associative recognition in the process of lymphocyte activation. (Lafferty & Gazda 1997, p 121)

They then describe how Matzinger's danger model is supported by findings relating to the allograft response in transplantation biology, and reiterate their support for it:

> We are now prepared to abandon the self/not-self basis of the immune system, replacing it with the danger metaphor as proposed by Matzinger. This danger metaphor focuses our attention on the process(s) of tolerance induction, not only in the neonate, but also in the adult animal. By doing so, new theoretical questions can be formulated and critically tested that are not centred simply around deletion of autoreactive clones. (Lafferty & Gazda 1997, p 122)

Further difficulties with the self/nonself discrimination model will be addressed during the discussion of Matzinger's danger model.

3.3 NETWORK THEORIES

3.3.1 JERNE'S IDIOTYPIC NETWORK THEORY

Until recently, Jerne's theory and its derivatives, has been the only alternative to self/nonself that has been regularly discussed in immunology journals. To explain his idiotypic network theory, Jerne developed a distinctive terminology. Some terms, such as "epitope" (for those parts of an antigen which contact the antigen binding site of an antibody or T cell receptor) have been taken into general use in immunology, others, such as "paratope" (for an antibody combining site) have remained characteristic of Jerne's theory. The terminology has not aided clear exposition of his theory. His original article (Jerne 1974) is obscure, and the following explanation is clearer than most:

> In the network theory of immune response regulation proposed by Jerne, the immune system is regarded as a web of variable domains based on interactions between idiotypes. The idiotype is the collection of idiotypes (*sic.* should read "idiotopes") found on any individual immunoglobulin molecule. The idiotype is an antigenic determinant found on the conformational structures. It distinguishes one set of antibodies from another. In the network theory, antigen elicits the production of antibodies (antibody 1) bearing idiotypic determinants that are able to induce synthesis of anti-idiotypic determinants of these anti-idiotypic antibodies (antibody 2). The idiotypic determinants of these anti-idiotypic antibodies can, themselves, elicit the production of other anti-idiotypic antibodies. The immune response is regulated by the suppressive action of the anti-idiotypic antibodies. The targets of suppression by anti-idiotypic antibodies are both the B- and T-cells. (Nakamura & Nakamura 1992, p 277)

This has prompted one researcher to complain that the

> . . . nomenclature [is] sufficiently daunting to keep popular understanding of the theory at bay indefinitely. (Haraway 1989, p 22)

However, the central concept is that the immune system is self regulating. Any

antibody molecule can act as antibody to an appropriate antigen, but also as an antigen for production of an antibody to itself (anti-idiotypic antibody). This occurs through the constant interactions of combining sites on both the antigens and antibodies (epitopes and paratopes). The result is that the immune system is in a constant state of internal response in readiness for an activating stimulus. Jerne's theory loses the dichotomy of self and nonself because the immune system is in a constant state of antibody and antigen interaction. What differs is the intensity of response when there is disruption to the homeostasis of the system.

Cohen (in Tauber 1998, p 465-467) takes this a little further and postulates that foreign antigens are not recognised because of their foreign-ness or difference (there are no identifiable chemical markers for this in any case (Cohn 1992, p 333; Dembic 1996, p 549)) but because they are presented in a context that declares them as pathological (presumably commensal microorganisms are tolerated because somehow they are not interpreted as being pathological). This notion is developed even further in Matzinger's danger model. One factor in favour of Cohen's theory is that it copes with the documented existence of temporary autoimmune reactions, such as those often found at the site of infections (George, Levy & Shoenfeld 1996; Nakamura & Nakamura 1992; Winfield & Jarjour 1991).

> The natural existence of autoimmunity negates a central principle of the clonal selection paradigm and suggests that the evolutionary aim of the immune system is not to distinguish self and nonself. In fact the aim of the immune system should escape no one; it is to enhance fitness [for survival]. (Cohen 1992, p 442)

Cohen's theory, like Jerne's, defines the operation of the immune system in a way that focuses on function rather than self/nonself discrimination.

3.3.2 COUTINHO'S NETWORK THEORY

This characteristic is also true of Coutinho's version (see Coutinho & Bandeira

1997, Varela & Coutinho 1991) although he preserves a place for the clonal selection theory while pursuing the network aspect of the immune system.

> . . . conventional immune responses and much of their regulation are satisfactorily explained by clonal selection principles . . . [Clonal selection] contributes the rational basis for anti-infectious protection. Instead, we suggest that the core operation of immune networks has little to do with immune responses, but is fundamental to the understanding of questions that were not solved by the clonal selection theory. (Varela & Coutinho 1991, p 159)

Coutinho's work stands out from the other theories presented in this chapter because he moves beyond the minutiae of cellular and molecular interactions to a meta-level where he examines the networking function of the immune system as a whole. He is interested in its "global properties".

> [They provide] a long-sought-for connection between different levels of description in biological phenomena . . . and can provide for immunologists . . . a detailed, precise account of emergent properties such as learning and memory, self tolerance, size and diversity of lymphocyte repertoires. . . . These global properties cannot be understood from the analysis of component parts only . . . As S. Ohno states "the state of current immunology can be summarised as knowing everything and understanding nothing." (1991, p 160)

Coutinho's work is of interest in that his network perspective brings to light many areas of immune function and cellular interaction that have been neglected or inadequately studied (Varela & Coutinho 1991). These include:

- The interactions between antibodies and lymphocytes in both neonates and adults, and how these vary between normal and autoimmune individuals.
- Interactions between the different types of T cells, and antigen independent reactions between T and B cells.
- The influence of lymphocyte activation on the immune system as a whole.
- The interaction of autoantibodies with other cells, and the process of their neutralisation with a view to moving beyond "primitive immunosuppression" as a treatment for autoimmune diseases.
- Implications of the natural fluctuations in antibody concentrations over time.

Coutinho still basically supports the notion of self/nonself discrimination, although he calls it self assertion. He holds that:

> . . . self is positively ascertained by the activation and recruitment of self -related clones into the dynamics of a densely-connected network, natural tolerance is dominant and the apparent unresponsiveness to self is positive for it reflects only a dynamic behaviour . . . (Varela & Coutinho 1991, p 165)

Coutinho's network theory is not intended as an alternative to self/nonself discrimination, or any other theory of detailed immune function, but stands as a useful reminder that immunology is a discipline where it is easy to get lost in minutiae and efforts should be made to maintain an awareness of the interconnectedness of components and their relation to the system as a whole.

3.3.3 NETWORK THEORIES AND LINGUISTICS

While these network theories have offered valuable insights into various aspects of the immune system, none of them has seriously been considered to offer a comprehensive alternative to self/nonself discrimination, at least not in the English speaking scientific world. It is interesting to contemplate here whether the debate has been influenced by linguistics. The English use of "self" as a noun, being

> . . . a person's or thing's own individuality or essence, person or thing as object of introspection or reflective action. (Sykes 1976, p 1030)

simply does not exist in many other languages. In Russian, articles on the issue carry titles such as "Ya ili nye ya" which translates as "Me or not me". (Petrov 1987, referenced in Silverstein 1997). In the French "Soi et non-soi", "soi" is a pronoun which refers generally to "oneself, himself, herself, itself" (Dubois et al 1955, p 226), but does not carry the reflexive connotation of the English usage. The same is true of the pronoun "selbst" in German. So perhaps the comments like the following by Cohn that

> . . . the French heretic school [eg Coutinho and colleagues] argues that the S/NS [self/nonself] discrimination does not exist so there is nothing to explain; instead . . . a global *gestalt* categorised as a "self-ish" or "self-conscious" or "self-referential" or "self-assertive" or "emergent" idiotype

> network, is proposed. This may be a comfortable language for some; now all we need is a valid precise conceptualization that deals with the behaviour of the immune system. (1992, p 331)

can be taken not as a criticism, but a statement of fact. For the French, and other linguistic groups, the self/nonself discrimination as perceived by speakers of English does not exist, and the use of “self” as an adjective or pronoun instead of a noun is indeed a comfortable language for some.

Immunology would be better served if these subtle cultural differences were appreciated and integrated into the dominant theories.

3.4 THE DANGER MODEL

The details of Matzinger’s danger model are given in her 1994 article “Tolerance, danger and the extended family.” The essence of the theory is that the primary function of the immune system is to recognise when elements of the body are being damaged or attacked, and then mount an appropriate response. This moves the immune system away from discriminating between self and nonself and into recognising cellular distress and unnatural cell death.

On a chemical level the shift is from recognising self-markers (widely acknowledged to be difficult if not “biochemically impossible” (Dembic 1996, p 549)) to recognising chemical signals of distress. These signals have not yet been conclusively identified, but are theoretically less difficult and Matzinger has postulated that they might involve heat shock proteins, a group of molecules that are released when a cell is exposed to environmental stress (Pennisi 1996, p 1667). Matzinger’s theory also adds a third signal to the two signal theories of Bretscher & Cohn, and Lafferty & Cunningham. The first signal occurs when a specific antigen is recognised by a T cell receptor (as in Bretscher and Cohn), and the second is the “costimulation” (of Lafferty & Cunningham) that is provided by antigen presenting dendritic cells. The third signal (added by Matzinger) is an alarm

from damaged or dying cells that activates the dendritic cells into delivering the second signal (Matzinger 1994, Pennisi 1996).

3.4.1 BENEFITS OF THE DANGER MODEL

One factor that weighs in favour of the danger model is that for many people, particularly students (and others who do not have a vested interest in preserving the traditional model), the danger model sits better at an intuitive level (Larkin 1997). It is easier to conceive that the immune system responds to a concrete and easily recognisable factor such as cell damage, rather than to a vague and ill-defined notion of "nonself - but only some of it".

As Matzinger herself puts it:

> When your skin is infected, or the liver has a problem, it sends a call to the immune system. It says, 'I am being damaged,' not 'I am being confronted with something foreign'. (Matzinger in Larkin 1997)
>
> [The] way a cell dies matters. There is programmed cell death, there is normal cell death, it goes on all the time, and then there is non-programmed cell death. And if you take the idea that it's bad cell death which triggers an immune response, you can explain almost everything that's out there, including hundreds of things that weren't explainable by self non-self. (Matzinger in Swan 1997)

These "hundreds of things" include: why a mother doesn't reject her foetus, which is half foreign (it is not causing damage and is not seen as dangerous), why the immune system does not respond to tumors (they are seen as growing tissue), why the immune system does not respond to all nonself items (it only responds to the ones that are causing damage), why lymphocytes are usually tolerant of the enormous range of self components, and particularly of those they haven't encountered before, either during their development in the thymus or later in the peripheral lymphoid tissue, and why the immune system is able to mount responses to some self components but does not usually do so.

Application of the model offers hope for improved tolerance of grafts in transplantation surgery. It also offers useful insights into the mechanism of autoimmune reactions, both transient and chronic, which the self/nonself discrimination theory finds so difficult to explain.

3.4.2 CRITICISMS OF THE DANGER MODEL

Not surprisingly the major critics of the danger model have generally been the foremost proponents of the self/nonself model. Langman & Cohn and Janeway attempt to reduce it to a detail of mechanism of the self/nonself theory. Silverstein, however, argues that it has all been said before and that the supposed threat to the ruling paradigm is “clearly hyperbole” (Silverstein & Rose 1997, p 199).

3.4.2.1 Langman & Cohn

Langman & Cohn scatter their criticisms of the danger model through several articles (primarily in Cohn 1998; Langman & Cohn 1996a; 1996b; 1997) with the most concentrated discussion in “Terra firma: a retreat from danger” (Langman & Cohn 1996b). In this article they claim that the theory has a key flaw,

> If anti-S Ab [anti-self antibody] does exist in normal healthy individuals, then at least some anti-S cannot be lethal. Because it is also experimentally demonstrable that lethal anti-S can be produced, and does kill, S-Ags [self antigens] have to be divided into lethal (L) and nonlethal (NL) classes. The defect in the logical underpinning of the ADR [Associative Danger Recognition - their term] model is that there is no basis for associating danger with NL-S-Ags, while not allowing danger to be associated with L-S-Ags. (1996b, p 4275)

They go on to apparently provide Matzinger’s defence, which in their words is that:

> . . . for the number of anti-S iT [inducible T cell - a mature cell that has not yet met antigen] and iB [inducible B cell] cells to be at sufficiently low levels, danger is rather rare, local, and transient. Thus, most anti-S iT and iB cells find S-Ag when danger is absent. Any anti-S that is produced in a focus of danger cannot continue to be produced after the danger has been removed by an immune response. (1996b, p 4275)

And they then try to reduce the danger model to self/nonself on the basis that:

> . . . the ADR model, in fact, requires quite an accurate S-NS discrimination at the level of the iT and iB cell repertoires. Any claim that the ADR model noes not require a S-NS discrimination is simply disingenuous. (1996b, p 4275).

It is true that Matzinger does put forward this argument, which in effect is saying that if there are any self-reactive lymphocytes roaming around they will only be activated against self components if there is a local danger stimulus. Once this stimulus is removed, once the would is healed or the infection is eradicated, the self reactive lymphocytes would cease to be activated. However Matzinger provides a far more detailed discussion of the issue than this implies.

To start with she carefully makes the distinction between autoimmune reactions and autoimmune diseases (Matzinger 1994, p 1033), a distinction that Langman & Cohn fail to address in their critique. Autoimmune reactions are a common and transient aspect of any immune response. They are more frequent early in a primary response, and decline later as the danger signal diminishes and any autoreactive lymphocytes present are tolerized by receiving signal one in the absence of signal two (the default OFF setting).

These autoimmune reactions may come from several sources and their effects may be harmful, harmless or useful. In a perfect system these autoimmune reactions should remain at a low level and fade out, but in a complex system like the human body there are many ways that things can go wrong, and some of these ways may lead to the chronic states of autoimmune disease. Matzinger also canvasses the hypothesis, extrapolating from the work of Bottazzo et al (1983):

> . . . that autoimmunity may not be a defect in the immune response but in the expression of antigen, either in its concentration, location, or way in which it is presented. This is not the same as the popular view that an autoimmune disease may be initiated by a disruption of immune regulation during the response to a foreign antigen that cross reacts with self.

(Matzinger 1994, p 1034)

This discussion of the aetiology of both autoimmune reactions and disease is entirely consistent with the notion of danger as an immune stimulus and does not require regression to a self/nonself discrimination. Langman & Cohn's arguments on these aspects are not convincing.

In their quest to reduce the danger model to a detail of mechanism of self/nonself discrimination they repeatedly make claims like the following:

> There is a general inability to define 'danger' other than by a set of conveniences that are indistinguishable from a set of nonself markers. (Langman & Cohn 1997)

It is difficult to see how the release of heat shock proteins or other some other signal of cellular distress or unprogrammed cell death can be interpreted as a nonself marker. It is a benefit of the danger model that it accommodates the immune reactions that occur as part of normal wound healing regardless of the presence or otherwise of foreign pathogens. The attempt of Langman & Cohn to deal with the threat the danger model presents to their own theory by defining it as "self", that is, as a detail of their own mechanism, is ultimately unsuccessful.

3.4.2.2 Silverstein

Silverstein takes a different line. His approach is basically to assert that it has all been said before and then throw all the theories out the window!

> . . . appeals to some type of teleological concept of the immune response such as Matzinger's "danger signal" or Janeway's "stranger signal" as the stimulus for activation of the immune response are unnecessary.. . . there is little evidence on which to conclude that the central issue in the evolution of the immune system is the distinction between self and nonself. (Silverstein & Rose 1997, p 204)

His basis for dismissing these and related theories is that:

> . . . all antigenic challenges obey the same rules. . . . all immunogenic substances activate the full measure of responses available to the immune system, both specific and non-specific. . . no recognitive component of the immune system, is able to discriminate between dangerous and innocuous stimuli. (Silverstein & Rose 1997, p 204)

But different immunogenic substances activate quite different responses. The immune response to an extracellular bacterium is quite different to the response mounted to an intracellular virus. The immune system does make very fine discriminations. Also Silverstein's assertion that "no recognitive component of the immune system is able to discriminate between dangerous and innocuous stimuli" is probably simply wrong.

Some nonpathogenic substances can elicit immune responses, but almost never do so in the absence of adjuvants that contain bacterial products (Fuchs, Ridge & Matzinger 1996). Janeway discusses this in detail, referring to the "immunologist's dirty little secret" (Janeway in Tauber 1998, p 460) being the need to use adjuvant material (mostly bits of killed bacteria) to obtain an immune response to various proteins and their conjugates. Janeway states that the belief that:

> . . . all foreign macromolecules are equally able to give rise to an immune response . . . is wrong. . . immunogenicity . . . requires both the presence of a suitable antigenic determinant to signal the lymphocyte through its antigen receptor and distinct signals derived from host cells. (Janeway 1989, p 5)

It is difficult, in any case, to envisage how Silverstein's version of the immune system would function, with all components of the immune system mobilised equally against every foreign invader, dangerous or otherwise. At a very fundamental level this does not account for the tolerance of commensal microorganisms, let alone do justice to the complexities of a highly specific and finely tuned network of cellular interactions.

3.4.2.3 Janeway

Janeway is a supporter of the self/nonself discrimination model. He accepts the findings of Matzinger and co-workers (Forsthuber, Yip & Lehmann 1996; Ridge, Fuchs & Matzinger 1996; Sarzotti, Robbins & Hoffman 1996) with regards to neonatal tolerance. He agrees that the findings of the three articles indicate that there is no "window" of neonatal tolerance, and that neonates are immunologically competent; that the differences in their responses is quantitative rather than qualitative. However he does not follow with support for her danger model. He asserts that although

> . . . no longer can we blithely speak of a window of tolerizablility in the neonate [they] have not, however, upset current paradigms of immunology. (Janeway, Goodnow & Medzhitov 1996, p 522).

Janeway stands out from other commentators because he critiques her experimental approach rather than just engaging in debate at a conceptual level. He claims that by using H-Y male antigen in female mice in her experiments on neonatal tolerance she is in fact demonstrating that a belief in self/nonself discrimination is integral to the design of "virtually all experiments in immunology" (Janeway, Goodnow & Medzhitov 1996, p 520). However, Matzinger claims that their experiment is entirely consistent with the danger model. They used the H-Y male antigen in female mice so that they could be sure that it was a protein the females' immune systems had never encountered before, it is also, apparently, a protein to which it has traditionally been hard to provoke a response. Their results were different to those previously obtained for two reasons: firstly they administered the antigen with a dose of antigen presenting cells (or dendritic cells) and secondly they claim that the surgery required to obtain the dendritic cells would have provided the activating danger signal (Pennisi 1996, pp 1666-67; Ridge, Fuchs & Matzinger 1996). Although the H-Y antigen was foreign to the female mice, the foreigness on its own was not a sufficient condition to provoke a response, there is far more required to provoke an immune response, therefore,

than just the presence of a foreign antigen.

3.4.3 THE DANGER MODEL SURVIVES ITS CRITICS

None of the criticisms of the theory so far have been convincing. It has the benefits of being able to explain many observations about the immune system for which the self/nonself discrimination model has been unable to account. As another sign of its merit, it is proving useful in areas such as oncology and transplantation surgery (Blumberg & Heal 1996; Lafferty and Gazda 1997), and is also now being referred to in articles on various aspects of immunology as a replacement for self/nonself discrimination (Colaco 1998; Gaston 1998; Nickoloff & Turka 1996; Uetrecht 1999). It also remains convincing when compared with the following range of recently offered alternative theories of immune function.

3.5 OTHER ALTERNATIVES

The following are examples of other theories of immune system function that have been proposed, or subject to some discussion in the last five years. Regardless of their merits they have not received the same attention as Matzinger's danger model, but then none of them have been set out with the same attention to the details of mechanism. One feature they generally share is a shift away from associating the function of the immune system with making the discrimination between "self and nonself" (whatever that might be). There is a trend towards seeing the immune system as involved in preserving homeostasis of cellular function. If the immune system is seen as making any sort of self discrimination it is that between "healthy" and "not healthy" cellular function. This is compatible with Matzinger's danger model, as her model details the mechanisms by which disturbances in cellular function and disruptions to homeostasis may be identified and dealt with.

3.5.1 JANEWAY'S STRANGER

Janeway holds to the central importance of the self/nonself paradigm. However he holds that the main evolutionary selection pressure exerted on the immune system was, until the recent advent of antibiotics, a microbial one. Other functions of the immune response such as graft rejection, tumour responses and autoimmune diseases have only seriously arisen this century. The immune system has therefore evolved to be activated by recognition of:

> Conserved patterns of molecules made by microbial pathogens but not by vertebrate cells. . . . The receptors for this signalling are known in some cases: the scavenger receptor expressed by macrophages and dendritic cells is one such case, but there are many others. (Janeway, Goodnow & Medzhitov 1996, p 521)

These are presented to T cells with an appropriate co-stimulatory signal.

This is very close to the associative antigen recognition theory of Cohn & Langman, except that Janeway claims that the recognition of nonself (or stranger) is easily accomplished because the immune system is genetically programmed to recognise certain types of distinctive foreign peptides. This correlates with the well documented immunostimulatory effect of various microbial molecules such as lipopolysaccharides, bacterial DNA and double-stranded RNA (Roitt, Brostoff & Male 1998, Ch10) and their use as adjuvants in vaccines.

Janeway's theory holds that the ability to recognise these molecules is an inherited trait, or "germline encoded". Cohn argues that although this germline encoding is characteristic of invertebrate immune systems, long-lived, peripatetic vertebrates are exposed to such a wide variety of pathogens that "a learned self/nonself discrimination became obligatory" (1992, p 323). The ability to recognise and respond to pathogens therefore continues to be developed by the immune system after birth. It is learned by the cells, or "somatically learned", rather than "germline

encoded". It is probable, however, that the vertebrate immune system operates with a mixture of the two.

Cohn also points out that proving the existence of some easily identifiable nonself (or stranger) markers on some microbial pathogens does not constitute sufficient grounds for a comprehensive theory for immune system function. It fails to explain the existence or mechanisms of autoimmunity.

Janeway's stranger model is therefore best seen, not as a comprehensive theory, but rather as an interesting elaboration of mechanism, bringing in a reminder that some aspects of immune recognition may be germline encoded rather than entirely somatically learned.

3.5.2 DEMBIC'S INTEGRITY

Dembic's integrity model (Dembic 1996) holds that the primary function of the immune system is to preserve integrity, or homeostasis of function. The molecular signals involved in this function are not necessarily involved in making a self/nonself discrimination, although aspects of this might be included in their operation.

Like the danger model, the integrity model postulates a third signal. The third signal in the danger model is an indicator of cellular distress, in the integrity model it is an indicator of disruption of homeostasis. Although Dembic provides a detailed account of the way the three signals operate "the question of the nature of the third signal remains open" (1996, p 549).

His main contribution is a subtle shift in the core axiom of the self/nonself discrimination away from the importance of "preformed defence" (1996, p 550).

> [The] immune system helps to preserve the state of balanced integrity of signals within any tissue, bodily part, or organism, and by doing so it learns to discriminate when disturbed. In conclusion, the reason why the immune system functions is the fundamental need to preserve self signals and not to discriminate the nonself from self, which is merely a consequence. (1996, p 550)

Dembic shares this perspective with Cunliffe, who instead of homeostasis, talks of morphostasis. Instead of danger, he talks in terms of preserving tidiness and clearing up the mess.

3.5.3 CUNLIFFE'S MESS

Cunliffe believes that it is not just time to redefine the primary function of the immune system, it is time to get rid of the concept of having an immune system.

> I believe that the conventional view has got it drastically wrong. The anamnestic T-cell system never was an immune system. It is a morphostatic system. (Cunliffe 1999, p 217)
>
> [The] conventional perspective misses important points. It is stalled on the idea that antigens are used to discriminate S [self] from NS [nonself]. Here, I argue that this emphasis on *antigens* is a quagmire conviction, bogged down in an outmoded perception. . . . the critical function of the immune (or morphostatic) system is the discrimination of healthy-self cells from other-than-healthy-self cells. (p 214)

While Cohn & Langman's adamant defence of the self/nonself discrimination is dismissed as being little better than a "flat earth" presumption, observing that "stale paradigms are held like religious beliefs" (p 213), Cunliffe's morphostasis perspective easily integrates Matzinger's danger model. In fact he talks readily of the notion of danger before converting it into "mess".

> Each zygote-derived cell is charged with monitoring and maintaining its own health. The overwhelming majority of all sick (dysfunctional) somatic cells are identified in house, within and by the disordered cell itself, using internal checkpoint controls. Sick cells (infected, aging, ectopic . . . etc.,) elect to apoptose [programmed suicide] on this internal realization of dysfunction: first they try to resolve the problem, but when this fails they trash their contents. Resident intracellular pathogens will be trashed in the process. . . . Immune aggression acts as a backstop - or mop up - mechanism that is poised to remember some caricature of sick cells that previously failed to successfully trash (and so sanitize) themselves. These

> cells and their debris are a *danger*.
> (p 214)

Cunliffe takes a similar line with the various types of autoimmunity. He also holds that the origin of immune memory is

> . . . rooted in the classification of whole cell death into safe or dangerous: the next time that similar cells are encountered, they can be left to get on with it themselves (for safely trashed cells) or encouraged to adopt a lowered threshold to apoptosis (for dangerous . . . cells). (p 214)

This idea is expanded in other papers (Cunliffe 1995, 1997), but the details are generally compatible with those outlined by Matzinger.

However, Cunliffe takes his terminology a step further, replacing *danger* with *mess* and *safe* with *tidy*.

> Now even the danger analogy becomes outmoded. . . The thymus-dependent immune system is a mess/non-mess discriminator and the whole morphostatic system is dedicated to maintaining a tidy household! (p 217)
>
> All cytoplasm has to remain membrane packaged, and preferably communicating, for it to be tolerated in the zygote derived colony: it is exquisitely simple. . . . Virtually by definition pathogens make a mess; but, there are many viruses and bacteria that don't make a mess. Anything is welcome . . . provided it doesn't make a mess or get in the way. (p 217)

Cunliffe's morphostasis complements Coutinho's emphasis on the network aspect of the immune system and the need to keep in mind its "global properties" and not just the minutiae of its functions. However Coutinho's work has focused on addressing the self/nonself discrimination, whereas Cunliffe finds the danger model more compatible.

3.6 TRENDS

The theories presented in this section have covered a variety of perspectives from supporting the status quo to discarding it completely. Some models, such as those

of the network theorists and Matzinger's danger simply sidestep the self/nonself issue. They find other ways of accounting for observed immune function, other criteria on which the immune system may discriminate. More recently still, the models of Dembic and Cunliffe show a trend towards seeing the maintenance of homeostasis or smooth function in the system.

One thing is very clear from this overview, and that is a general movement away from the traditional self/nonself discrimination model. A viable future probably lies in a melding of the danger model with a homeostasis model such as that by Dembic or Cunliffe, while keeping a "global perspective" on the way the immune system interacts with other biological systems in the body .

3.7 IMPLICATIONS FOR PAEDIATRIC VACCINES

3.7.1 ADJUVANTS

Taking the emphasis off identification of nonself antigens and transferring it to danger throws the emphasis very heavily on the adjuvants used in vaccines. Where most modern vaccines are concerned there is an increasing interest in using cell-surface peptides and fragments of DNA (Ada 1994b; Butts 1998; Donnelly & Ulmer 1999; Eko et al 1999; Ellis 1994b; Elliott et al 1999; Gellin 1998; Gregoriadis 1995; Haynes 1999; Kowalczk & Ertl 1999; Mor 1998). These on their own are not going to provide sufficient danger or disruption, it is the adjuvant that will provide the stimulus for the response. Currently aluminium compounds (aluminium phosphate and hydroxide) are the only adjuvants licensed for humans, and there are recognised problems with their use. Many new adjuvants are in development and they will need to be reviewed with reference to these recent developments in immunological theory. This issue will be dealt with in Chapter 4.

3.7.2 NEONATAL TOLERANCE

The findings on neonatal tolerance as reported in *Science* (Forsthuber, Yip &

Lehmann 1996; Ridge, Fuchs & Matzinger 1996; Sarzotti, Robbins & Hoffman 1996) have been widely acknowledged to have revised previous beliefs about the existence of a “window” of neonatal tolerance. They have shown that the foetal and infant immune system is only quantitatively different to the adult system, not qualitatively different. These experimental findings, and the concurrent shift in theory have significant repercussions for the design and dosage of paediatric vaccines and will be dealt with in Chapter 5.

3.8 CONCLUSION

This shift in immunological theory has profound implications for the creation and administration of vaccines. It is no longer sufficient to rest in the belief that administration of any appropriate nonself antigen (plus maybe a bit of adjuvant to help it along) is going to provoke an adequate and protective immune response. The constant reports of vaccine failures in healthy individuals and lack of correlation between antibody count and protective immunity have been showing this for a long time (see Chapters 2 & 8).

Vaccines designers will need to think more along the lines of “What will provide the immune system with an appropriate danger signal to associate with this antigen?”, “What will provide a suitable disruption to the homeostasis of the system in a way that retains memory of the event?” Instead of concentrating on trying to identify characteristic markers of foreignness (eg bacterial cell-surface molecules) there may be a role for employing a wider range of inter-cellular co-stimulatory molecules.

CHAPTER 4

ADJUVANTS

In general it appears that the body of knowledge regarding mechanisms of adjuvancy or adjuvant effect could better be described as voodoo or witchcraft. (Kenneth R. Brown. Merck Research Laboratories, Pennsylvania. 1995, p 245)

4.1 INTRODUCTION

As recently as 1989, Cohn observed that:

> Any view of immune behaviour, . . . which cannot in principle confront the problem of class regulation [between cell-mediated (Th1 type lymphocytes) and humoral immunity (Th2 type lymphocytes)] is patently unproductive. Both the conceptual and practical consequences of the solution to this problem are so far-reaching that they should reflect the major concern of immunology. Very rarely in the construction of vaccines, for example, is manipulation of the class of response considered, although it most assuredly makes the difference between success and failure. (1989b, pp xxxvii-xxxviii)

Immunologists involved in vaccine design have since become very aware of this issue, however the technicalities of producing the desired response, and

determining its effectiveness, have proven complex (see for example Allison 1995; 1998; André 1999; Brewer & Alexander 1997; Del Giudice, Pizza & Rappuoli 1998; Dintzis 1992; Gaines Das 1999; Kovarik & Siegrist 1998; Lindberg & Pillai 1996; Nossal 1997; Raychaudhuri & Rock 1998).

Original vaccine formulations, such as those for diphtheria, measles, mumps, rubella, polio, pertussis and tetanus, took the relatively simple approach of attenuating or inactivating a pathogen. Exposure to this weakened or killed pathogen ideally provoked an immune response very similar to that of the wild pathogen, but without the virulence and associated risk. However, because it lacks the virulence of the wild pathogen, the attenuated or inactivated form does not necessarily provide the required "danger" signal. This problem is even more pronounced with the current trend in vaccine development that focuses on purified components of pathogens as these are often very weak immunogens (Audibert & Lise 1993). To overcome this an adjuvant is often included in the vaccine (Bomford 1998; Donnelly 1997).

"Adjuvant" comes from the latin word *adjuvare*: to help or to aid. Immunological adjuvants are a diverse range of chemical compounds that have little else in common other than their ability to help stimulate an immune response. They include mineral salts, mineral and organic oil emulsions, bacterial and viral products (Audibert & Lise 1993).

Adjuvants may be used to increase either the cellular or humoral response to an antigen by eliciting an early, high and long lasting response. Their inclusion may decrease the amount of antigen required, particularly if the antigen is a weak immunogen (Gupta & Siber 1995), this may also reduce side effects by minimising the amount of potentially toxic antigenic material needed in each dose. Their

inclusion may even reduce the number of injections required (Donnelly 1997). Both a reduction in amount of antigen, and fewer trips to the physician for injections helps to minimise the cost of the vaccination (Gupta et al 1993; Donnelly 1997).

4.2 MODE OF ACTION

Although a wide variety of adjuvant compounds are available, and many are being investigated for human use, it is still acknowledged that very little is known about their mode of action, as testified in the following quotes:

> There is an increasing trend away from classical attenuated or killed whole pathogen vaccines towards developing chemically defined preparations. Paradoxically, in order to be effective, these defined vaccines require incorporation into adjuvants, of which very little is actually understood about how or why they work. (Brewer & Alexander 1997, p 233)
>
> While the number of substances with adjuvant activity and the literature describing their use has expanded enormously, their mode of action has remained largely mysterious and empirical. (Cox & Coulter 1997, p 248)
>
> Most of the adjuvants that have been tested preclinically have been discovered empirically and their mechanism of action is poorly understood. In addition, preclinical studies have shown that most conventional adjuvants support the generation of some kinds of immune responses but fail to elicit other important arms of the immune response such as cytotoxic T lymphocytes. (Raychaudhuri & Rock 1998, p 1025)

Some general principles of their operation have been defined, although the details are uncertain. They include immunomodulation, presentation, targeting and depot formation.

4.2.1 IMMUNOMODULATION

This refers to the effect the adjuvant has on the cytokine balance. Most commonly an adjuvant will stimulate the production of some cytokines at the expense of others, and this will determine whether the response is predominately humoral (Th2) or cell mediated (Th1):

> The immune system never swings totally in one direction or the other. The most notable swings are produced by aluminium salts >90% Th2 and

> bacterial endotoxins and derivatives (Lipid A, monophosphoryl lipid A) which induce a predominately Th1 type response. (Cox & Coulter 1997, p 248)

This ability to influence the balance of cytokines is an important consideration in paediatric vaccines, and particularly so in vaccines that will be used at birth, or for neonates. This will be examined in more detail in Chapter 5.

4.2.2 PRESENTATION AND TARGETING

Presentation is:

> . . . the ability of an adjuvant to preserve the conformational integrity of an antigen and to present this to appropriate immune effector cells. (Cox & Coulter, p 249)

A significant technical difficulty is that most injected vaccine formulations remain in the extra-cellular fluid and are thus presented on MHC class II molecules and only able to elicit a T helper response. To be presented on MHC class I molecules and elicit a cytotoxic T lymphocyte response, the antigens in the vaccine would need to enter the cytoplasmic compartment of the cell. Research is therefore being conducted into “Trojan horse” viruses which may be able to introduce antigens into the required cells (see for example Nossal 1997; Aron-Maor & Shoenfeld 2003).

Targeting is the process of delivering the antigen to the appropriate immune effector cells, and:

> Although little data exists, it is likely that the vast majority of vaccine delivered is lost either by . . . degradation or by . . . removal in the liver. (Cox & Coulter 1997, p 250)

To overcome this may require that the adjuvant efficiently targets antigen presenting cells, or that it preferentially saturates various cells in the liver so that the antigen is left free to be taken up by the antigen presenting cells (Cox & Coulter 1997).

4.2.3 DEPOT EFFECT

It has been generally held that adjuvants have a depot effect, that is, they hold antigen at the site of inoculation, where its slow release prolongs the immune response. However, recently this view has been largely discredited by findings that:

- the adjuvant has the same effect if injected separately from the antigen at a different site (Mitchison 1993).
- most of the adsorbed antigens have been displaced from the adjuvant within 15 mins following injection (Heimlich et al 1999).
- excision of the antigen depot shortly after injection has little effect on the resulting immune response (Brewer & Alexander 1997).

The ability of the adjuvant to stimulate the cells of the draining lymph node is therefore more important than a reservoir of adjuvant at the injection site.

If the influence of an adjuvant is systemic rather than localised, this has repercussions for the practice of administering several paediatric vaccines simultaneously, because it implies care should be taken to ensure, as far as possible, that the adjuvants used in one vaccine will not interfere with the immune response to the other vaccines. For example, it is known that one of the most commonly used adjuvants, aluminium hydroxide, reduces antibody response to Hib conjugate vaccines, but aluminium phosphate does not (Eskola et al 1999; Kovarik & Seigrist 1998). In the current Australian Immunisation Schedule (NHMRC 1997) the licensed DTP acellular vaccine contains aluminium hydroxide and this can be administered at the same time as Hib (PRR-OMP) which is a conjugate vaccine that also contains aluminium hydroxide (NHMRC 2000a). On this issue Eskola et al acknowledge that the combination of Hib conjugates with DTPa vaccines has led to lower antibody responses. They conclude that:

> Although the mechanism of this interference needs to be studied in more detail, we believe that the finding does not have major clinical implications . . . the lowered antibody concentrations are not associated with altered priming of memory function. The advantages of combination vaccines, mainly the need for fewer injections and immunisation visits, should be balanced against the weaknesses, such as the perceived

concerns about interaction and lower antibody titres. (1999, pp 2066-67)

However they add the caution that:

> Because of several unanswered questions relating to the mechanism and clinical significance of the interference in antibody concentration, controlled and carefully monitored introduction of these combination vaccines, as has been done in Germany, would be prudent. (1999, p 2067)

The complexities of evaluating vaccine response and efficacy will be dealt with in Chapters 8 & 9.

4.3 DESIRED QUALITIES IN AN ADJUVANT

Safety is the primary consideration when including an adjuvant, particularly into paediatric vaccines. This ideally involves meeting requirements such as:

- minimal local reactions.
- lack of toxicity or induction of systemic reactions.
- minimal hypersensitivity reactions.
- lack of carcinogenicity.
- stability of formulation in conjunction with the antigen.
- ability to elicit protective immune response even with weak antigens.
- effectiveness in infants and neonates.
- biodegradable and non-immunogenic on its own.
- does not induce or exacerbate autoimmune diseases.
- stability during storage and transport.
- can be manufactured consistently.

(from Gupta & Siber 1995, p 1264)

None of the currently available adjuvants meets all these criteria, and it is recognised that:

> . . . the absolute safety of adjuvants can never be guaranteed. It appears that the toxicity can be ascribed in part to the unintended stimulation of various mechanisms of the immune response. Consequently, safety and adjuvanticity must be balanced to get the maximum immune response with minimum side effects. (Gupta et al 1993, p 300)

4.4 LICENSED ADJUVANTS

The aluminium salts, aluminium hydroxide and aluminium phosphate, are still the only adjuvants licensed for human use in the United States (Heimlich et al 1999; Kovarik & Siegrist 1998; Vogel 1998), and the only ones in the paediatric vaccines licensed for use in Australia (NHMRC 2000a), although France still favours the use of calcium phosphate (Léry 1994). There are limitations with the use of aluminium adjuvants, and so the potential of many other formulations is being examined (Gupta et al 1993; Gupta & Siber 1995). Some are candidates for human use, and a selection of these will be briefly discussed later.

In their favour, aluminium salts are credited with a good safety record. They fit the criteria of low reactogenicity and induction of good antibody response, although some local reactions do occur and increase with subsequent exposure. Their long history of use makes them difficult to replace. They are also inexpensive (Cox & Coulter 1997).

A significant problem with the preparation of aluminium adjuvants is that they are difficult to manufacture in a "physico-chemically reproducible way, thus resulting in batch to batch variations" (Gupta, 1998, p 156). A review in the 1960's revealed that:

> . . . specifications are practically nonexistent for controlling the chemical purity of the aluminium compounds used in the preparation of adjuvants for biologic products. (Piersma 1966, p 353)

To overcome this, in 1989, the World Health Organisation chose Alhydrogel, an aluminium hydroxide compound from Superfos Biosector in Denmark, as the standard preparation for inclusion in vaccines (Gupta et al 1995).

Another limitation of aluminium salts is that they are not active with all immunogens (Audibert & Lise 1993), and do not promote a cell mediated Th1 or cytotoxic T-lymphocyte response. They promote only a humoral, or Th2 lymphocyte response in both mice and humans, which is accompanied by the generation of IgE-mediated allergic reactions. This

> . . . Th2 driving activity of aluminium salts is, therefore, a major disadvantage for infant vaccines aiming at the induction of Th1 and CTL [cytotoxic T lymphocyte] responses to viral/bacterial agents. Such Th1 responses, which are difficult to elicit in early life, will be, furthermore, driven towards Th2 responses in the presence of aluminium salts. This could be of significant importance for certain new vaccines as the priming effect of this Th2-polarizing alum formulation could only be partially reverted even by boosting at adulthood with a strong Th1-driving adjuvant. (Kovarik & Seigrist 1998, p 226)

Particular care needs to be taken with this issue when multiple vaccines are administered simultaneously. An example of this problem is found in the Australian Childhood Immunisation Schedule (NHMRC 2000a) where the aluminium salts, aluminium hydroxide and aluminium phosphate, are used as adjuvants in both the whole cell and acellular DTP vaccines. These are administered simultaneously with OPV which requires a Th1 or cell mediated response to promote protective immunity. Further to this, the promotion of related IgE responses has relevance to the development of atopic or allergic conditions as will be discussed in Chapter 7.

Another concern with the use of aluminium adjuvants is their association with neurological conditions. Aluminium plays no known biological role in the body, and tends to accumulate in the tissues of the liver, kidney, spleen, bone, brain, heart and hair (Allen & Cumming 1998).

> Aluminium has long been associated with neurological changes, especially Alzheimer's disease. Aluminium causes changes in neuron structure and a breakdown of electrochemical neuro-transmission. Most of the research was done with Alzheimer's patients and autopsies of brain tissue of affected individuals. It is only reasonable to suspect the immature brain structure of a small baby to be extremely vulnerable to aluminium compounds injected

> into its system. (Griffin 1998, p 103)

The Provisional Tolerable Weekly Intake (PTWI) of aluminium as set by the Joint Expert Committee on Food Additives (World Health Organisation 1989) is 7mg of aluminium per kg of body weight.

> The usual dose of aluminium used for human vaccines is around 0.5 mg. The upper allowable limit of aluminium adjuvants for injection in humans is 1.25 mg as per World Health Organisation regulations and 0.85 to 1.25 mg aluminium as per United States Food and Drug Administration guidelines. (Gupta 1998, p 161)

In the Australian Immunisation Handbook (NHMRC 1997) the conjugate Hib vaccine PedavaxHIB from CSL/Merck, Sharp & Dohme is noted as containing 225 µg of aluminium per dose. Four injections (at 2,4,6 and 12 months) are required to complete the schedule.

The DTP whole cell vaccine (Triple Antigen by CSL) is adsorbed onto aluminium phosphate, and the DTP acellular vaccine (Infanrix by SmithKline Beecham) is adsorbed onto aluminium hydroxide. Although no mention is made of the amount of aluminium included in each dose either in the Handbook or in the product inserts for these vaccines, presumably it is within the WHO guidelines. Five injections (at 2,4,6 and 18 months, and at 4-5 years) are required to complete the schedule.

The Hepatitis B vaccine (Engerix-B by SmithKline Beecham) contains 0.5 mg/ml pf aluminium hydroxide. The paediatric dose is 0.5 ml, providing 0.25 mg aluminium. The schedule requires three injections. The initial dose is followed by another one a month later, and a final one six months later. Hepatitis B has been endorsed for all infants at birth (with follow up injections at 1 and 6-12 months) and is “strongly recommended” (NHMRC 2000a, frontispiece) if the mother is HBsAg+ [hepatitis B surface-antigen positive] and/or if the mother belongs to a group with a carrier rate of over 2%. This is a large proportion of the world’s population including Aboriginal

and Torres Strait Islanders, people from Asia, Africa, Oceania, Central and South America, Eastern Europe and the Mediterranean (NHMRC 2000a).

The cumulative total of aluminium in the paediatric schedule is therefore only a few grams and “minor compared to that of diet and medications, such as antacids” (Gupta 1998, p 165). However a major difference lies in the route of administration.

With the oral route, only a small percentage of the total ingested aluminium is absorbed into the body. The amount of aluminium absorbed from the gastrointestinal tract may be influenced by a variety of factors including the

> . . . overall composition of the diet and potential moderating effects of particular ions such as citrates, silicates, fluoride and phosphates and other substances . . . (Allen & Cumming 1998, p 11)

The details of this influence are not clearly understood, however, it is known that

> . . . not all forms of dietary aluminium are available for absorption and that potential sites of absorption will differ throughout the gastro-intestinal tract. . *In vivo* measurements suggested that only a small portion of aluminium is potentially available for absorption throughout the small bowel . . . (Allen & Cumming 1998, p 54)

In contrast, when a dose of vaccine is injected into muscle tissue, all the aluminium present must be dealt with by the body. It is the lymphatic system, rather than the gastrointestinal tract that would be called upon to disperse and eliminate the aluminium in this situation. However, many aluminium compounds, including aluminium hydroxide and aluminium phosphate, are insoluble (Penney 1995) and are not biodegradable (Gupta 1998). Aluminium adjuvants have been found at the injection site in mice and guinea pigs up to one year later (Gupta 1998).

> . . . studies suggest that children who had primary immunization with aluminium-adsorbed vaccines are more likely to develop antigen specific Ig E and higher frequency of local reactions on booster injection with soluble or aluminium adsorbed vaccines than children who had primary

immunization with unadsorbed vaccines. (Gupta 1998, p 165)

Findings such as these, and the connection of the systemic accumulation of aluminium with nervous system disorders and bone diseases have led some scientists (such as Gupta 1998; Mark et al 1975) to suggest the "need to re-evaluate aluminium compounds as vaccine adjuvants" (Gupta 1998, p 165).

4.5 OTHER ADJUVANTS

Many new types of adjuvants are undergoing preclinical trials for human use. The diverse range of compounds reflects the assertion by researchers such as Cox & Coulter (1997) and Raychaudhuri & Rock (1998) that their discovery is mainly empirical, and their mode of operation poorly understood. There are hundreds of adjuvant compounds, here I have presented a classification of the four main types, with a selection from each that are notable because they are significant candidates for human use, or have already been used in experimental vaccines:

- chemical adjuvants
  - mineral compounds
  - polymer microspheres
  - cytokines
  - liposomes
- plant derived adjuvants
  - saponins
  - immunostimulating complexes (ISCOMS)
- bacterial/viral adjuvants
  - lipopolysaccarides
  - recombinant bacterial ghosts
  - "Trojan horse" viruses
- emulsions as adjuvants
  - non-metabolizable oils
  - metabolizable oils

4.5.1 CHEMICAL ADJUVANTS

4.5.1.1 Mineral compounds

Other mineral salts such as zinc sulphate, colloidal iron hydroxide, calcium chloride and calcium phosphate can be used as adjuvants (Gupta et al 1993). France favours the use of calcium phosphate, because it is biodegradable, promotes high

amounts of Ig G with less Ig E than aluminium compounds (Gupta et al 1993) and does not induce sensitivity with repeated exposure as is the case with aluminium compounds (Léry 1994). However, aluminium salts are still favoured by the World Health Organisation, the United States, Australia, and many other countries (Gupta et al 1993).

4.5.1.2 Polymer microspheres

This is the same technology that provides slow release of various drugs into the body, for example in the treatment of cancer. Synthetic polymers have been developed which create microspheres that provide slow release of the antigen. To do this the polymers are dissolved in solvent, mixed with antigen, and then the solvent is removed to yield microspheres which encapsulate the antigen. The polymers break down in the body, thus providing slow release of the antigen (Cleland 1995). They have potential to be administered orally for booster doses of previously injected antigens (Hanes, Chiba & Langer 1995). Problems include solvent removal and consistency and control of manufacture (Cox & Coulter 1997).

4.5.1.3 Cytokines

These are the chemical messengers found naturally in the body that regulate the function of both T and B lymphocytes. When being discussed with reference to their potential role as an adjuvant they may be referred to as “genetic adjuvants” (Kowalczyk & Ertl 1999, p 760). Those under consideration for vaccine use include:

CYTOKINE	**ACTION**
IL-1 [interleukin-1]	T and B cell maturation.
IL-2	Th1 stimulation.
IL-4	Th2 stimulation.
IL-12	Th1 stimulation.
IFN-γ [interferon gamma]	Th1 and MHC stimulation
GM-CSF [granulocyte-macrophage colony-stimulating factor]	Macrophage and dendritic cell stimulation.

(from Cox & Coulter 1997; Donnelly 1997)

IFN-γ and IL-2 have been trialled in a hepatitis B vaccine (Audibert & Lise 1993).

IL-12 and GM-CSF are also being extensively researched (Heath 1995; Openshaw & Hussell 1998).

Although they are a natural component of the human body there are many problems to overcome before they can be effectively included in vaccines. These include high production costs, lack of stability, a very narrow window of effective concentration, rapid inactivation by naturally occurring inhibitors in serum and tissue fluids, toxicity, and association with autoimmune reactions (Audibert & Lise 1993; Cox & Coulter 1997; Dong, Brunn & Ho 1995; Donnelly 1997; Hughes 1998),

> Because cytokine and costimulatory genes encode self-molecules, the possibility of eliciting autoimmune response to these molecules should not be underestimated. (Haynes 1999, p 18)

4.5.1.4 Liposomes

Liposomes are "vesicular bilayer structures generally composed of phospholipids and cholesterol" (Pietrobon 1995, p 349) in an aqueous suspension that are sometimes used as vehicles for the administration of drugs. They have a similar permeability to biological membranes (Glück 1995), and they can incorporate both water soluble and lipophilic antigens (Allison 1997). They are biodegradable and do not produce significant local or systemic reactions (Pietrobon 1995). The primary adjuvant effect of liposomes is macrophage stimulation. Macrophages are the antigen presenting cells found in tissues. There is evidence that they may play a role in cytotoxic T lymphocyte responses (cellular immunity) as well as humoral immunity. They are also thought to have a depot function because they offer long-term antigen release.

> Liposomes may be constructed in such a way that antigen is still being released at the time that immunological memory has been firmly established. (van Rooijen, p 15)

They have been used in many experimental vaccines (Allison 1995) and the only

major manufacturing consideration is the need to ensure careful removal of the organic solvents and/or detergents that are employed during the process (Glück 1995).

> Because of the large experience and enormous knowledge about liposomes as adjuvants and because of the general absence of toxicity, liposomes may be the first candidates to replace alum as the classical adjuvant. (Glück 1995, p 327)

4.5.2 VEGETAL ADJUVANTS

4.5.2.1 Saponins and Immunostimulating complexes (ISCOMS)

Quil-A is a saponin extracted from the tree *Quillaia saponaria*. It has been used in veterinary vaccines, but on its own it is unsuitable for human use because it is haemolytic and causes severe local reactions. When further purified it becomes water soluble and loses most of its toxicity. It is then known as QS21. When mixed with cholesterol and antigen, it forms structures called immunostimulating complexes or ISCOMS (Werner & Jolles 1996).

ISCOMS stimulate both humoral and cell mediated responses to a large number of antigens.

> Iscoms enhance immune responses in various ways, including increased MHC class II expression on antigen-presenting cells, induction of IL-1 production, activation of helper and cytotoxic T cells and generation of potent long-lasting antibody responses. The experimental conditions, however, for incorporation of different antigens and Quil A into iscoms have in general been empirical. (Bengtsson & Sjölander 1996, p 753)

> ISCOMS have been shown to stimulate both humoral and cell-mediated response particularly . . . CTL response (MHC class I) . . .(Gupta & Siber 1995, p 1271)

They have not yet been approved for human use, mainly because of uncertainties in the manufacturing process (Bengtsson & Sjölander 1996) and concerns about the side-effects of Quil-A, “although these side-effects were almost absent when

Quil-A was incorporated into ISCOMS" (Gupta & Siber 1995, p 1271).

4.5.3 BACTERIAL/VIRAL ADJUVANTS

4.5.3.1 Lipopolysaccharides

Lipopolysaccharides are molecules found in the outer membranes of gram-negative bacteria. It is thought that they activate B and T-cells and antigen-presenting cells (Donnelly 1997), and that they work because

> . . . they mimic the microbial structures that have provided the danger signal of infection from the beginning of the evolutionary history of host defences. (Audibert & Lise 1993, p 282)

They are too toxic for use in human vaccines, although they are present in the whole cell vaccines for pertussis, cholera and typhoid, which have been used in humans for many years (Gupta & Siber 1995). Infants less than 18 months of age have ineffective immune responses to lipopolysaccharide antigens, which is presumed to be related to the absence of certain subpopulations of B lymphocytes in the early months. This has been overcome by the use of polysaccharide-protein conjugate vaccines such as Hib-tetanus or Hib-diphtheria (Pietrobon 1995).

4.5.3.2 Recombinant Bacterial Ghosts

In addressing the complex problem of recombinant vaccine technology, Eko and colleagues claim that:

> It is no longer desirable mixing together existing vaccines and trying to overcome chemical and immunological obstacles for the combinations used. (1999, p 1644)

They advocate the use of bacterial ghosts (empty cell envelopes) to provide a vehicle for the administration of a wide range of antigens in a manner that is versatile, stable, easily administered, and effective early in life.

To accomplish this they use Gram-negative bacteria, where cloning of a particular gene results in the formation of a tunnel structure in the cell wall and lysis of the

cell contents. The empty cell membrane is called a “ghost” and foreign proteins can be attached to the inside of the inner membrane. Ghosts can therefore act as carriers of foreign antigens, immunomodulators or other substances and be used as “carriers or targeting vehicles or as adjuvants in combination with subunit vaccines” (Eko et al 1999, p 1643).

They have two main benefits. The first is that they can be administered orally, by aerosol, or by injection, suspended only in water or saline. They are therefore able to induce a broad and “naturally” stimulated immune response without the need for the use of other adjuvants, stabilisers or a cold-chain.

> . . . analysis of immune responses in different animal models indicates that ghosts induce humoral and cellular immune responses against cell envelope constituents including protective (mucosal) immunity against challenge infections. (Eko et al 1999, p 1645)

The second benefit is that their preparation does not involve any “inactivation procedures that denature relevant immunogenic determinants” (Eko 1999, p 1648) and this ensures the quality of the antigen being presented. Recombinant bacterial ghost technology therefore has great potential in overcoming some of the considerable problems that are being encountered with the development of multicompontent vaccines.

4.5.3.3 “Trojan Horse” viruses

These are “harmless” viruses that can be genetically modified to carry proteins from other viruses into the cells of the body where they can produce a long lasting immune response. Sendi virus envelopes have been used in Phase I clinical trials (see Section 8.1 for details on clinical trials) on experimental AIDS vaccines (Gellin 1998, Appendix C), and the Kunjin virus has been used to carry proteins from viruses such as Hepatitis C. The Kunjin virus is related to the yellow fever virus, but does not induce the death of the cells it infects. It has

> . . . allowed [antigenic] proteins to be produced at high levels in the body for a long time without damaging other cells and [was] safe because the virus could not escape from the cells. (Stock 2000)

This is promising technology, but at least five years away from general human application.

4.5.4 EMULSIONS AS ADJUVANTS

4.5.4.1 Non-metabolizable oils

Freund's complete adjuvant has been in use since the 1930's. It contains killed mycobacteria in a mineral-oil (paraffin) and water emulsion. It is too toxic for human use, and in laboratory animals it induces severe side-effects that include abscess formation at the injection site, severe pain, permanent organ injury and autoimmune disease (Gupta et al 1993).

Freund's incomplete adjuvant (without the killed mycobacteria) is used in several veterinary vaccines. It was initially used in a few human vaccines, such as influenza and inactivated polio but was discontinued because of side effects such as abscess formation, although the influenza vaccine continued to be administered to United States armed forces for some time (Beebe, Simon & Vivona 1964). Now, however, it has been

> . . . concluded that the use of mineral oil adjuvants in the human population may be hazardous and should not be recommended for general use in humans. (Gupta et al 1993, p 294)

However it is now in use again in several experimental AIDS vaccines (Gellin 1997, Appendix C).

4.5.4.2 Metabolizable oils

As a result of the toxicity associated with mineral oil emulsions, various other oils have been investigated. One group of vegetable oil emulsions used either peanut oil or sesame oil mixed with Arlacel A (the ester mannide monooleate) as the emulsifier and aluminium monostearate as a preservative. These oils were considered less toxic than mineral oils because they break down into glycerol and free fatty acids, and can be cleared from the body.

However, with the peanut oil, care had to be taken to ensure it was not contaminated with aflatoxin B1, a toxin from a mould which grows on peanuts and can be carcinogenic (Gupta et al 1993), and use of Arlacel A was discontinued when it was reported to be carcinogenic in some strains of mice (Allison 1995).

Recently much attention has been paid to the use of emulsions, in water, of squalene or squalane. Squalene is a naturally occurring precursor of cholesterol, while squalane is a saturated and more stable form that occurs naturally in sebaceous secretions. They are thought to have a similar effect to that of liposomes, and appear to promote a cell mediated or Th1 type immune response (Allison 1997). They are the basis of adjuvants such as SAF, Ribi adjuvant, and MF59 (Allison 1995).

Of these, MF59 and SAF have appeared promising for human use (Gellin 1998).

> MF59 is a safe, practical, and potent adjuvant for use with human vaccines. The formulation is easily manufactured . . . and is both compatible and efficacious with all antigens to date. MF59 has been shown to be a potent stimulator of cellular and humoral responses to subunit antigens in both animal models and clinical studies. Toxicology studies in animal models and Phase I-III studies in humans have demonstrated the safety of MF59 . . . (Ott et al 1998, p 294)

However, “squalene has been used extensively as an adjuvant in animal models to induce autoimmune diseases” (Asa, Cao & Garry 2000, p 61). Recent research

into Gulf War Syndrome, “a multisystemic illness affecting many Gulf War-era veterans” (Asa, Cao & Garry 2000) showed that 95% of overtly ill troops who were deployed, and 100% of those who were immunized but not deployed, had antibodies to squalene. Antibodies to squalene were not detectable in the general public, or in Gulf War Veterans who were not ill.

Two control subjects who volunteered to participate in a vaccine trial at the United States National Institutes of Health developed a multisystem disorder similar to that of Gulf War Syndrome. The trial involved the use of a squalene-containing adjuvant. One person

> . . . received a single injection and became ill within 3 weeks, with signs and symptoms including arthritis, fibromyalgia, lymphadenopathy, photosensitive rashes, fatigue, headaches and fasciculations. This patient had lower than normal acetylcholinesterase and histological evidence of IgG-mediated demyelinization. The NIH vaccine study code was broken; only adjuvant containing squalene had been administered as a placebo. . . . [The second person] went through the complete experimental vaccination protocol before manifesting a similar set of signs and symptoms and was +3 for ASA [anti-squalene antibodies]. (Asa, Cao & Garry 2000, p 62)

The study therefore suggests “evidence of an immune factor based upon the adjuvancy of squalene” (p 62) in the aetiology in these cases of multisystemic illness, and this would indicate that great care needs to be taken with the use of even apparently “natural” adjuvants. This is for two reasons. Firstly there are considerable variations in individual immune responses, and secondly adjuvants are designed to stimulate the immune system, and in such a complex system it is possible, that in some individuals, an adjuvant may act to upset the balance of various mechanisms which regulate autoimmune responses, thus leading to autoimmune disease (Nakamura & Nakamura 1992; Shoenfeld & Aron-Maor 2000).

4.6 CONCLUSION

To make vaccines safer for use, especially in infants, the focus in vaccine development is moving away from simply attenuating or inactivating pathogens and towards using purified subunits of the antigens. These purified subunits are, however, much weaker immunogens, and to provoke an immune response strong enough to provide lasting immunity, it is necessary to combine the antigen with an adjuvant.

During the last decade there has been an increasing awareness of the different classes of immune response, and the need to ensure that the class of response provoked by the adjuvant is complementary to the antigen being administered. This has been accompanied by an awareness of the enormous complexities of this endeavour.

Aluminium and calcium compounds are still the only adjuvants licensed for human use, with aluminium compounds in primary use. Aluminium compounds have limitations and are associated with some health concerns. Many new and innovative adjuvant compounds and technologies are being evaluated for human use. Some have already been included in experimental vaccines.

The range of potential adjuvants is vast and varied, and it is not clearly understood how they operate. Their discovery and evaluation is therefore empirical.

> In the absence of a true understanding of the mode of action by which adjuvants mediate their effect on vaccine responses, their influence on vaccine-driven antibody responses is being analysed quantitatively. . . and qualitatively . . . (Kovarik & Siegrist 1998, p 226)

The nature of their usefulness is also the basis of the main cause for concern about their use:

> Immunological adjuvants have the generally desirable property of eliciting cell-mediated immunity and antibodies when administered with an antigen.

> They may also cause a more generalized and indiscriminate stimulation of the immune system and disrupt the balance of immune self-regulatory mechanisms, which may lead to autoimmune disease. (Asa, Cao & Garry 2000, p 61)

On this count it would appear that the more mechanical methods of adjuvanticity such as recombinant bacterial ghosts and the use of “Trojan viruses” may be safer than the use of chemical compounds, even biodegradable compounds natural to the body such as squalene and cytokines, as it is these chemicals which are most prone to disrupting the delicate chemical balance of the system. Despite the need for new adjuvants to replace or augment the use of aluminium compounds, and to cope with the need for combination vaccines, much care is being taken over the licensing of new adjuvants for this reason.

CHAPTER 5

NEONATAL TOLERANCE

5.1 INTRODUCTION

It has long been recognised that the neonatal immune system differs from that of the adult, but the nature and extent of these differences still requires clarification. Studies “have led to various and conflicting conclusions” (Andersson et al 1981, p 5), and it is still acknowledged that “our knowledge about T lymphocyte responses in human newborns is limited” (Marchant et al 1999, p 2249). This is mainly because of technical difficulties in obtaining data, which include:

- Small sample sizes.
- Inaccuracy of extrapolating findings from other animals such as mice and sheep. (Hayward 1981)

- Inaccuracy of extrapolating from in vitro findings.
- Variations in results from using different types of chemical analysis.
- Variations in interpretation of experimental results. (Miyawaki 1981)

- The small quantities of blood available for analysis.
- Influence of various maternal immune factors, such as IgG and transferred antibodies. (Andersson et al 1981)

However, an increasing number of vaccines are being administered either at birth or in the first couple of months of life (currently BCG, HBV, DTP, Hib and polio) and there is interest in *in utero* vaccination (particularly for tetanus), either directly or by vaccination of pregnant women (Ada 1994a; Ahman 1998). It is important, therefore, that the unique characteristics of the neonatal immune system be clearly

understood as a rational basis for the design of effective vaccines. This is despite assertions such as that made by Lawton (1994) that:

> [Neonatal v]accine design is likely to remain empirical for some time and should not be impeded by theoretical concerns, such as a fear of tolerance or the search for the single best T-cell epitope. (p 154)

Until recently it was widely accepted that susceptibility to tolerance was one aspect of the neonatal immune system that set it apart from the immune system of an adult.

5.1.1 DEFINITION

Immunological tolerance is a state of unresponsiveness to a particular antigen that has been induced by prior exposure to that antigen (Roitt, Brostoff & Male 1998; von Herrath & Whitton 2000). It differs from the general state of immunosuppression. Tolerance is antigen specific and does not impair the immune response to other antigens, whereas immunosuppression is a depression of the immune response to a wide variety of antigens. Immunosuppression is usually transient, whereas tolerance may be transient or permanent (Goust, Tsokos & Virella 1993). Neonates have seemed particularly prone to developing tolerance in response to antigens.

The most significant consequence of the tendency of neonates to develop tolerance to foreign antigens is rarely spelled out in the scientific literature on vaccines. However, if an infant becomes tolerant of a foreign antigen, on subsequent exposure later in life they may be unable to mount a satisfactory immune response to that antigen, and the infection may become chronic. This has been demonstrated experimentally in mice, and has also been observed in human infants particularly with regards to hepatitis B (Milich et al 1990; Schodel, Peterson & Milich 1996).

The classical view regarding neonatal tolerance dominated immunology for nearly fifty years (from 1950 until 1996). It held that, because of its immaturity, the neonatal immune system is qualitatively different to that of an adult, and is uniquely susceptible to developing tolerance to foreign antigens. Recently this view has been challenged, and new experimental findings have implications for the development and administration of paediatric vaccines.

5.2 THE CLASSICAL VIEW

The classical view of tolerance in the neonatal immune system originated with the work of Owen (1945). He showed that twin cattle born from a single placenta "freemartin cattle", who had exchanged blood cell precursors *in utero*, were tolerant of the foreign antigens from their twin. They did not reject blood transfusions, as would be the case with twins from separate placentas who had not been exposed to these foreign antigens *in utero*. This observation was developed by Burnet & Fenner (1949) into the theory that the immune system learns to recognise "self" antigens by a process of actively acquired self-tolerance that involves the deletion of self-reactive T cell clones. In the 1950's Medawar and colleagues showed that the tolerance of freemartin cattle extended to skin grafts, and followed through with experiments on mice to develop the notion of "neonatal tolerance".

In the classical view of neonatal tolerance:

> The embryonic and neonatal periods have been thought of as a window in ontogeny during which the developing immune system is particularly susceptible to tolerization. Thus, antigenic challenge in neonatal life may result in specific T cell unresponsiveness in the adult. (Grabie & Karin, p 907)

The rationale behind this was that the embryonic and neonatal periods constitute the time when the immune system is learning to recognise what is "self", and delete

any self-reactive T cell clones. At this time the developing immune system was believed to be at risk of defining any foreign antigens present as “self” and tolerating them, rather than defining them as “foreign” and mounting a response (Langman & Cohn 1996).

However, many experiments done since the 1950’s have called into question the very simplicity of

> Burnet and Medawar’s simple notion that tolerance was acquired because of a special state of immune cells *in utero* and in neonates. (Janeway, Goodnow & Medzhitov 1996, p 519)

The central notion that tolerance to self is actively acquired was still respected, but it was suggested that other factors such as the amount of antigen and association with other immune stimulating factors might be more important in determining the immune response than just the time of administration (Janeway, Goodnow & Medzhitov 1996). This view has come into general acceptance since the publication of three prominent articles in an issue of *Science* in 1996.

5.2.1 IMPLICATIONS FOR PAEDIATRIC VACCINES

Under the classical view it was believed that to overcome this susceptibility to tolerance it was necessary to administer large doses of antigen to elicit a satisfactory response (Pennisi 1996), and that if a neonatal vaccine was found not to elicit a satisfactory antibody response scientists explained it in terms of having “misjudged the window of neonatal tolerance and given the antigen at the wrong time . . . they used that as a convenient way to hide the inconsistencies” (Bendelac in Pennisi 1996).

5.3 THE NEW VIEW

In 1996 three papers (Forsthuber, Yip & Lehmann; Ridge, Fuchs & Matzinger; Sarzotti, Robbins & Hoffman) were published in an issue of *Science* that built on

previous research to significantly change the classical view of neonatal tolerance. They showed that the neonatal immune system was capable of protective immune responses, provided the antigens were presented in a manner that made them available to appropriate antigen-presenting cells.

Sarzotti, Robbins & Hoffman found that:

> The inability of neonates to develop a CTL [cytotoxic T lymphocyte] response to high doses of virus was not the result of immunological immaturity but correlated with the induction of a nonprotective type 2 cytokine response. Thus, the initial viral dose is critical in the development of protective immunity in newborns. (p 1726)

Forsthuber, Yip & Lehmann re-examined the "classic system for induction of neonatal tolerance to protein antigens" (p 1728) and found that:

> The presumably tolerogenic protocol trigger[ed] a vigorous T helper cell type 2 (Th2) immune response. . . Neonates are not immune privileged but generate Th2 or Th1 responses, depending on the mode of immunization. (p 1728)

Ridge, Fuchs & Matzinger used the results of their experiments with dendritic cells to conclude that:

> For some time it has been thought that antigenic challenge in neonatal life is a tolerogenic rather than immunogenic event. Reexamination of the classical neonatal tolerance experiments of Bilingham, Brent, and Medawar showed that tolerance is not an intrinsic property of the newborn immune system, but that the nature of the antigen-presenting cell determines whether the outcome is neonatal tolerance or immunization. (p 1723)

Part of the reason for the shift in perspective is that these scientists were working from, or at least influenced by, Matzinger's "danger" model rather than the traditional paradigm of "self/non-self discrimination" (see Chapter 3).

> Our theoretical basis . . . suggests that the immune system does not discriminate between self and nonself but between dangerous and harmless entities, and that the primary distinction is made by antigen-presenting cells,

> which are activated to up-regulate costimulatory molecules only when induced by alarm signals from their environment . . . (Ridge, Fuchs & Matzinger 1996, p 1723)

The main contribution of the three papers mentioned above is that immunologists can "no longer . . . blithely speak of a window of tolerizability in the neonate" (Janeway, Goodnow & Medzitov 1996, p 522). They demonstrate that the neonatal immune system does not show unique susceptibility to the induction of tolerance to antigens, and is not so remarkably different to that of the adult. They suggest instead that what appears to be a fundamental difference is, in fact, the result of a combination of subtle differences in the signalling requirements of inevitably inexperienced cells which operate as

> . . . an adaptive mechanism to optimise survival by balancing the conflicting immunologic requirements of life *in utero* with those of the external environment. (Schelonka & Infante 1998, p 12)

A detailed analysis of the function of different types of antigen-presenting cells is a feature of these studies. They also examine the implications of the way in which the cell profile of the immune system of a neonate differs from that of an adult.

The following is an outline of the current understanding of the differences in signalling requirements for neonatal lymphocytes, and an explanation for the associated observation of tolerant states.

5.3.1 DIFFERENCES BETWEEN THE NEONATAL AND ADULT IMMUNE SYSTEMS

There are quantitative differences between the neonatal and adult immune systems. The total lymphocyte count and the percentage of T and B cells do vary with age. They are higher at birth, continue to increase during the first six months of life and then gradually decrease to adult levels by 13-21 years of age (for

detailed discussion see: Heldrup, Kalm & Prellner 1992; Hicks et al 1983). However the activation requirements of the inexperienced lymphocytes in the neonatal immune system are a far more significant feature, as they hold the explanation for the observation of neonatal tolerance.

The immaturity of the neonatal immune system means that as many as 97% of T cells will not yet have come into contact with foreign antigen (Schelonka & Infante 1998). Mature T cells (of any class) which have which have not yet met with antigen are sometimes known as “virgin” or “naïve” T cells, whereas “experienced” T cells have responded to antigen at least once.

When appropriately stimulated by antigen presenting cells, the naïve T cells of the neonate are able to act as T helper cells, but require “a greater array of activation signals than adult T cells” (Schelonka & Infante 1998, p 9) to achieve this. That is, they need the presence of more costimulatory signalling molecules on the surface of antigen presenting cells. Therefore neonatal T cells rely on specialised antigen presenting cells, such as dendritic cells, to stimulate proliferation and production of cytokines, whereas adult T cells can be stimulated by signals from B cells as well (Matzinger & Guerder 1989). Dendritic cells are rare, comprising only 1-3% of spleen, whereas B cells are far more common, about 60% of spleen (Matzinger 1994; Schelonka & Infanta 1998).

When activated, in comparison with adult cells, neonatal T helper cells show reduced production of cytokines. This is particularly the case with IL-2 and interferon-γ for Th1 cells, and IL-4 for Th2 cells. The reduced production of IL-4 means that neonatal Th2 cells are poor stimulators of B cell immunoglobulin production. Lower levels of interferon-γ affect the development of cell-mediated immunity, important in fighting viral infections. The reduced production of IL-2 by Th1 cells has a cyclical effect because it is IL-2 that in turn stimulates the clonal

expansion of more T lymphocytes, and the activity of T helper cells (Goldman, Ham Pong & Goldblum 1985; Schelonka & Infante 1998). The reduced production of IL-2 by T lymphocytes is of particular note because it limits their ability to operate and proliferate.

Although both naïve and experienced T cells are activated by dendritic cells, naïve T cells differ in that they are tolerized by B cells, whereas experienced T cells are activated by B cells (Matzinger 1994). In terms of responding to activation signals, this means that a naïve T cell will die, or be rendered inactive, if it receives signal one (the OFF signal) in the absence of signal two, but it can only receive signal two (the ON signal) from specialised antigen presenting cells such as dendritic cells. It cannot receive signal two from B cells, whereas experienced T cells can. This is because signal two on specialised antigen presenting cells is enhanced by the presence of costimulatory molecules. (See Section 3.2.2 for a detailed discussion of signals).

One possible reason for this, argued on theoretical grounds, is that it helps to prevent dangerous autoimmune reactions. The immunoglobulin molecules on the surface of B cells mean they are 10 to 10^4 more effective than other antigen presenting cells at capturing and presenting antigen, which makes them particularly useful at the end of primary immune responses and at the beginning of secondary ones, when the concentration of antigen is very low (Matzinger 1994). They also hypermutate when stimulated. A B cell mutation could become specific for a common self-component (serum component, or cell surface protein). T cells are tolerant of self-components at normal concentration, but the autoreactive B cell could concentrate a self-component to the point where T cells respond to it (presumably reading the unnatural concentration as a danger). If the B cell could activate naïve T cells,

> . . . they would initiate unstoppable autoimmune responses. The simplest way to prevent this type of autoaggression would be to require that virgin T cells be activated first by a professional APC [antigen presenting cell] before they can interact effectively with a B cell. (Matzinger 1994, p 1009).

In newborns the proportion of B cells is greater than T cells, "and these [B] cells increase to up to five times the adult number by age 6 months" (Goldman, Ham Pong & Goldblum 1985, p 76) which makes neonatal naïve T cells particularly susceptible to tolerization by B cells.

The secret to producing an effective response from naïve neonatal T cells is to ensure presentation of antigen is made by specialised antigen presenting cells such as dendritic cells, and to administer the correct dose of antigen to support this.

Sarzotti, Robbins & Hoffman (1996) examined the effect of different concentrations of antigen on the neonatal immune response. They found that:

> The newborn and adult immune systems have a vastly different number of T cells, and if newborns are injected with adjusted doses of virus or antigenic cells or a similar type of adjuvant, they react like adults. (Sarzotti 1997, p 49)

The reason why doses of antigen that are either too low, or too high result in tolerance induction is explained by Matzinger (1994, p 1013) as follows:

<u>a) Very Low Doses</u>

At very low concentrations, antigen is captured mainly by antigen-specific B cells, because they

> can be thousands of times better at capturing antigen than other APCs [antigen presenting cells]. (Matzinger 1994, p 1013)

As it is mostly B cells presenting antigen, any naïve T cells that come into contact

with them will be rendered tolerant.

b) High Doses

At high doses, the antigen will be captured nonspecifically by all B cells (not just the antigen-specific ones). These B cells comprise about 60% of spleen compared to professional APCs which make up 1-3% of spleen, and the result will again be tolerance.

c) Low to Medium Doses

At medium doses, the antigen will be captured by professional APCs which out number the antigen-specific B cells, and some naïve T cells will be activated. This will lead to a competent immune response and effective immunisation.

5.3.2 IMPLICATIONS FOR PAEDIATRIC VACCINES

In the past the approach to paediatric immunisation has been to administer large doses of antigen in an attempt to overcome neonatal tolerance. These studies have shown however,

> . . . that the proper amount of antigen is key to successful vaccination and that vaccination failure in infants may be due to too high a dose of antigen. (Pennisi 1996)

This has been confirmed in studies on a variety of vaccines. For example Marchant et al (1999) in a study on the tuberculosis vaccine BCG, found that the "immune response to vaccines can . . . be influenced by . . . the dose of Ag [antigen] administered." (p 2253)

> The Th-1 type immune response induced by BCG in newborns is likely to be dependent on the activation of APCs [antigen presenting cells]. Dendritic cells are the APCs involved in the initiation of primary immune responses. Mycobacteria, including BCG, infect dendritic cells and markedly increase their ability to present Ags to T cells. This higher Ag-presenting capacity is related to an increased expression of costimulatory surface molecules and cytokines like IL-12. (p 2253)

These findings have led Marchant et al (1999) to propose potential uses for BCG vaccine that include the deliberate use of it to stimulate Th1-type immune responses in newborns to help prevent the development of atopic states associated with a predominantly Th2 immune profile (see Chapter 7 for a detailed discussion of this issue) and using BCG as a vector for other foreign antigens.

When researching antibody responses to an experimental vaccine with pneumococcal polysaccharides conjugated to tetanus toxoid, Ahman et al (1998) found that the "concentrations of Hib and tetanus toxoid antibodies decreased significantly as the dose of PncT vaccine increased" (p 2731) and they suggested the reasons for this might include the following:

> First, the high load of tetanus toxoid may induce T-cell tolerance during the primary series. Second, the high dose of polysaccharides may interfere with antigen processing and/or presentation through alteration in the intracellular transport of MHC II peptide complexes during the primary series. (p 2731)

Lower doses were also found to be advantageous in the practice of vaccine administration. In New Zealand in the early 1980's a paediatric course of plasma-derived hepatitis B vaccine (3 doses of 10μg) cost NZ$75, placing it beyond the reach of the national health budget. They trialled using one fifth of the dose (3 doses of 2μg) and found it to be

> . . . remarkably immunogenic with anti-hepatitis B antibody mean geometric titres of about 1000 IU/L. (It is generally considered that levels of ≥10 IU/L are protective). (Goldwater 1993, p 222)

They were then able to effectively vaccinate the population for NZ$15 per child. This was one fifth of the cost of the dose recommended by the manufacturers, and still produced an antibody level one hundred times that required for protection. Follow up studies showed establishment of an effective immunological memory, even when hepatitis B antibodies had fallen to low levels (Moyes, Milne & Waldon

1990). These findings were confirmed by Goldfarb et al (1996) who compared the effects of 5 and 10-μg doses. They found that although the 10μg dose gave a greater concentration of anti-hepatitis B antibody, the seroprotection rates (antibody levels $\geq$10 mIU/ml) were identical, and they suggested further studies to determine whether the concentration of antibody had any influence on long-term memory.

5.4 CONCLUSION

Since 1996 there has been a significant shift in the way the neonatal immune system is viewed. It is no longer seen as being uniquely susceptible to immunological tolerance. The prevailing dogma no longer holds that large doses of antigen must be administered to overcome this inherent resistance to antigen response, in fact this practice has been implicated in the induction of tolerant states. Instead, the neonatal immune system is viewed as functionally similar to that of an adult and capable of the same range of responses. The observed differences are explained because there are slightly different proportions of various cells and necessarily more “naïve” lymphocytes than are found in an adult. These naïve lymphocytes have particular requirements before they can be activated, and exposure to too little, or too much antigen can render them tolerant. This has significant repercussions for determining the dose of antigen in vaccines. Already researchers are finding that in many cases a vaccine dose lower than previously thought necessary, is proving equally, or more, effective.

CHAPTER 6

IMMUNOLOGICAL MEMORY

6.1 DEFINITION

Immunological memory is one of the defining features of the immune system. It is the ability of the immune system to mount a faster or more intense response to a second or subsequent stimulation by the same or similar antigen.

> The establishment and long-term maintenance of immunological memory underpins all protective vaccination strategies. (Müllbacher 1994, p 314)

A clear understanding of the mechanism of immunological memory, and an effective means of measuring it, would therefore be of assistance in the rational design of vaccines and the evaluation of their efficacy. Unfortunately, as detailed below, scientists do not have such an understanding. There is considerable debate about the mechanisms involved in the development and maintenance of immunological memory, and the available data appear to raise more questions than they answer, as evidenced by the following range of quotes from immunologists

publishing in this field:

> The subject of immune memory has been extensively studied, but there is still considerable debate regarding the mechanisms by which protective immunity is maintained. (Ahmed & Gray 1996, p 54)

> Answers to fundamental questions . . . still elude us and preclude a fuller understanding. (Gray 1994, p 425)

> Browsing through textbooks and authoritative texts quickly reveals that the definition of immunological memory is not straightforward. . . . The identification of essential cellular parameters needed for this memory reaction is far from complete, and whether memory as measured in vitro is relevant for protective immunological memory in vivo remains an open question. (Zinkernagel et al 1996)

> These observations have aroused considerable controversy. (Sprent 1997, p 259)

> Many studies have been performed and many hypotheses have been proposed, however, they are somewhat inconclusive. (Vongsakul 1995, p 75)

> All of the above hypotheses concerning the mechanism of immune memory seem reasonable. (Guan & Qi 1995, p 715)

Even providing a clear definition of immunological memory is not as easy as it seems, because although ‘the ability of the immune system to mount a faster or more intense response to a second or subsequent stimulation by the same or similar antigen’ sounds straightforward, problems arise as soon as we are asked to define what is meant by ‘response’ and how it may be measured. The following table gives a range of reasonable definitions and appropriate methods for their assessment:

MODES OF ASSESSMENT OF IMMUNOLOGICAL MEMORY

POTENTIAL CRITERIA FOR ASSESSING MEMORY	MODE OF ASSESSMENT FOR THIS CRITERION
1. Antigen induced reactive state of the immune system.	Comparison of *in vivo* "responses" to first and subsequent challenges with the antigen.
2. Extent of lymphocyte proliferation maintained independent of antigen.	T cell precursor frequencies measured by limiting dilution analysis.
3. Change in the "physiological character" of the cells.	Measurement of changes in cell surface markers and secretion of various lymphocytes.
4. Level of protection against secondary *in vivo* challenge by a pathogen.	Measurement of kinetics of infection in primed hosts or in adoptive transfer experiments (very difficult to measure).

(compiled from Zinkernagel et al 1996, p 341)

The technical details involved here are not important, what is important to note is the range of functions subsumed in immunological memory, and the very different ways in which the associated parameters may be measured, and that there exists no consensus on the most accurate or effective method. The literature in this area is complicated by this lack of consensus:

> The reports of differential lymphokine production by naïve and memory T cells are contradictory and therefore confusing; this is entirely predictable unless everyone uses a large (and preferably the same) panel of markers to identify the particular subset or activation stage under investigation. (Gray 1993, p 63)

Often researchers are measuring very different aspects of the immune system under the single umbrella of "memory" without making clear the exact parameters of their particular definition (Mitchison 1992; Vongsakul 1995; Zinkernagel et al 1996).

The level of uncertainty regarding immunological memory has even prompted one author to observe that:

> . . . if the host has survived initial infection with a virulent virus, it will inevitably survive secondary infection, which poses the troubling question of whether memory is really essential or merely represents an epiphenomenon! (Sprent 1997, p 260)

6.2 THE MAIN THEORIES

There are three main theories on the maintenance of immunological memory. They are:

1. Some lymphocytes (T and B cells) respond to antigen by differentiating into “memory cells” with a much longer life-span than other lymphocytes. It is not clear what mechanisms are involved in this putative transformation (Müllbacher 1994).
2. Memory cells have a lower threshold for stimulation than other cells. This is partly because they have different levels of various adhesion molecules on their surface, and can be easily activated by periodic exposure to environmental antigens (Ahmed & Gray 1996; Gray & Matzinger 1991). This theory, however, does not account for maintenance of long-term memory in the absence of re-exposure to antigen (see Section 6.3).
3. Memory relies on the persistent presence of antigen, rather than on the nature of the responding cell. Antigen is periodically reintroduced by recurring infections, or is maintained in reservoirs, for example it may be held on the surface of the follicular dendritic cells found in the lymphatic system, and this acts to maintain stimulation, or production of appropriate memory cells (Ahmed & Gray 1996; Gray & Matzinger 1991; see Section 6.4).

There is merit in each of these theories, and in reality immunological memory is probably a complex blend of all of them, plus other mechanisms as yet undefined. However, the situation is further complicated by the existence of the belief that immunological memory comprises both short-term and long-term memory.

6.3 SHORT-TERM AND LONG-TERM MEMORY

Short-term and long-term memory are not clearly defined in the literature, and their definition is complicated by the fact that most of the experiments are conducted on the murine immune system, and it is not always easy to extrapolate findings to a

relevant human time scale (Slifka et al 1998). However, in reference to humans, short-term memory is rarely defined, but is usually taken to be days or a couple of weeks, and long-term memory is generally a month or more (Colle, Truffa-Bachi & Freitas 1988).

It is believed that short-term and long-term immunological memory exist as distinct but complementary systems. The main reason for this belief is that we are exposed to such a wide range of pathogens it does not seem possible for the immune system to maintain life-long memory for all of them, and indeed the immune system does not. It is believed that long-term memory is required to protect against virulent but rarely encountered pathogens, and that short-term memory is required to deal with the range of pathogens constantly encountered in the immediate environment. However, this situation is complicated by the tendency of pathogens to evolve. This is particularly the case with viruses that mutate rapidly, for example influenza viruses, but is also true of more slowly evolving evolving pathogens such as measles or polio (Luria & Delbrück 1943).

However, a primary question here is ‘On what basis does the immune system select the pathogens to which it maintains a long-term memory?’ This question can usefully be viewed in terms of the logistics of information storage.

> The question is about the dilemma facing a homeostatic immune system. Like librarians with limited shelf space, who must decide whether to keep old seldom-used texts or replace them with more current titles, the immune system must either keep memory T cells against rare antigens, though they may never again be needed, or make space for expansion of lymphocytes against pathogens in the immediate environment. (Matzinger 1994, p 605)

It is believed that the mechanisms involved in short-term and long-term immunological memory are different (Matzinger 1994).

6.3.1 SHORT-TERM MEMORY

Matzinger holds that short-term memory is partly a function of the follicular dendritic cells (FDC's) of the lymphatic system, which bind antigen on their surface. During the initial infection with a pathogen, for example a virus, T and B cells specific to that virus are formed to help clear the infection. It is postulated that some antigen becomes bound to the surface of local FDC's and then is slowly released. Once released, this antigen is captured by the virus specific B cells, which process and present them to the memory T cells. This keeps the response going for some months, although it will eventually wane as the store of antigen on the FDC's is used up.

If the pathogen is common in the environment, the constant restimulation provided by repeated exposure will maintain the short-term memory. However, if the pathogen is rare, the short-term memory response will eventually disappear and any subsequent reinfection will elicit the same response as an initial infection. This appears to be what happens particularly with localized mucosal infections such as rotavirus, respiratory syncitial virus (RSV) and various rhinoviruses (Ahmed & Gray 1996). This may be one reason why it has proven difficult to formulate effective vaccines for these pathogens.

6.3.2 LONG-TERM MEMORY

Long-term immunological memory has been known about for centuries. The evidence for its existence is based on the traditional observation that individuals who have survived a virulent disease rarely succumb to it again. The Greek historian Thucydides, when writing about the plague of Athens in 430 BC noted that "the same man was never attacked twice" (Finley 1951).

Detailed documentation of long-term immunological memory was obtained in the isolated Faroe Islands. Severe measles epidemics occurred sixty-four years apart,

in 1781 and in 1846. The second epidemic was carefully documented by Panum, a Scandinavian surgeon, who observed that only individuals older than sixty-four who had measles during the earlier epidemic, did not contract the disease. This made the important point that immunity could be sustained in the absence of apparent re-exposure to the virus (Ahmed & Gray 1996; Matzinger 1994).

Long-term memory tends to be associated more with systemic infections. These are infections that involve the immune system as a whole, as opposed to a localized infection of, for example, the mucosal tissues of the respiratory tract. Systemic infections include diseases such as measles, yellow fever, polio, mumps and small-pox. These are diseases for which the most effective vaccines have been made, although generally the protection offered by these vaccines is not as long-lasting as that provided by natural infection (Ahmed & Gray 1996; Mackay 1993; Matzinger 1994). To understand why this is so will require a much better understanding of the mechanisms involved than currently exists, as even:

> The reasons for the marked differences in the durations of mucosal versus systemic antibody responses are not known. (Ahmed & Gray 1996, p 59)

There are currently two main theories on the maintenance of long-term memory. One holds that it relies on the existence of long-lived cells that do not require ongoing exposure to specific antigen for their maintenance or survival, and the other that long-term memory depends on the persistent presence of antigen regardless of how long the memory cells might live. Both theories have significant problems and probably only constitute a partial explanation of an obviously complex situation (see for example: Ahmed & Gray 1996; Gray 1993; Gray 1994; Mackay 1993; Matzinger 1994; Sprent 1997).

6.4 DOES LONG-TERM MEMORY REQUIRE THE PERSISTENCE OF

ANTIGEN?

Some immunologists treat the debate as being polarized between those who argue that long-term memory does require the persistence of antigen (Gray & Matzinger 1991; Matzinger 1994), and those who argue that it doesn't (Hou et al, 1994; Müllbacher 1994). There exists experimental evidence for both sides, although the experiments are technically challenging, and the results are open to interpretation. However, there are other viewpoints (Mitchison 1992; Slifka & Ahmed 1998; Swain et al 1996) and other relevant issues, such as the existence of long-lived plasma cells (Slifka et al 1998) and the role of nerve growth factor (Fuchs 1996). Consideration of these aspects makes the details of this debate relevant to much broader issues. Particularly, they are relevant to immunisation.

6.4.1 EVIDENCE THAT MEMORY REQUIRES PERSISTENCE OF ANTIGEN

Any discussion of this issue is complicated by its relevance to both T and B cells, even though the two cell-types have different roles and functions, and complex interactions.

> The duration of immunological memory may differ for the T and B cell systems. (Mackay 1993)

> The existence of memory B cells has been well recognised for decades, contrary to memory T cells which are comprised of various subpopulations. Therefore, greater controversy exists concerning the role of memory T cells in the immune response than about the role of memory B cells. (Vongsakul 1995, p 75)

However, evidence has been presented that both B cells (Gray & Skarvall 1988) and T cells (Gray & Matzinger 1991) require the persistent presence of antigen for the maintenance of memory.

Gray & Skarvall note that:

> . . . the fact that an individual may continue to make an antibody response for many months following a single injection of antigen is often overlooked. This continued antibody production is probably due to repeated stimulation

> of antigen-specific B cells [which] require antigen for their maintenance. (1988, p 71)

In their experiments, memory B cells were apparently lost from the adoptive host mice after 10-12 weeks in the absence of stimulating antigen. This is in agreement with previous reports (Celada 1967; Celada 1971; Feldbush 1973), however all these experiments suffer from concerns about the inadvertent transfer of antigen with the cells.

Gray & Skarvall hold that memory is not maintained by long-lived cells in a resting state, because

> . . . present findings indicate that memory B cells in this resting state are deleted from the recirculating pool within a matter of weeks unless they meet antigen again. (Gray & Skarvall 1998, p 72)

Instead they hold that it is maintained by the clones (or offspring) of antigen specific cells that continually replicate. The replication of these clones is maintained for a long time by constant stimulation with the small amounts of antigen that are held on the surface of follicular dendritic cells which are located primarily in the lymphoid tissues.

A selection of immunologists support this position on B cells and have either reviewed it favorably (Mackay 1993) or used it as a theoretical basis for research work (for example MacLennan, Garcia de Vinuesa & Casamayor-Palleja 2000; Paroli et al 2000). Guan & Qi (1995) found this theory the most rational basis for their mathematical model of the secondary immune response. They chose it over the hypothesis of long-lived resting cells, and also over the hypothesis that immunological memory is not a function of a particular type of cell, but rather a function of the system as a whole. However, even though they favored the clonal theory, Guan & Qi conceded that “all of the above hypotheses . . . seem

reasonable" (1995, p 715) thus acknowledging the high degree of uncertainty associated with immunological memory.

Gray & Matzinger present evidence that a similar situation exists with respect to T cells.

> Both helper and cytotoxic T cells maintain their ability to generate secondary responses only in the presence of original priming antigen. (Gray & Matzinger 1991, p 969)

They believe that memory works by maintaining a continuous level of cell activation and division, rather than by using very long-lived cells.

Gray & Matzinger (1991) assert that their experimental findings provide proof for the hypothesis that memory relies on long-lived clones rather than long-lived cells. However, there are significant areas of uncertainty that are highlighted by their results.

To start with, they admit that they do not know what actually happens when a memory cell is exposed to persisting antigen. Although there is evidence that antigen is stored on the surface of follicular dendritic cells, it is not clear how it can be processed to provide the peptides necessary for stimulation of the relevant T and B cells (Hou et al 1994). It is not known what form this stimulation takes, or the effect it has on the memory cell, they even

> . . . do not know whether each new encounter of a memory cell with persisting antigen leads to cell division . . . [or] simply allows survival. (Gray & Matzinger 1991, p 972-73)

They also note that their failure to detect a response in the absence of antigen "may only reflect lack of specific T cell help during the in vitro restimulation" (1991, p 972), and their particular experimental procedure meant that even in their in vivo experiments they

> . . . cannot rule out the possibility that the loss of CTL [cytotoxic T lymphocyte] response is a reflection of a lack of specific T cell help. (1991, p 972)

The interpretation of these experiments also exposes various technical problems. For example, they are unable to rule out that "a very small number of memory cells are truly antigen independent" (p 971), or that a small amount of antigen was inadvertently transferred. There is the "possibility of generating *in vitro* artefacts" (Müllbacher 1994, p 320), that is, patterns of cell reaction that result from the conditions that the cells are exposed to during the experiment, that would not normally occur *in vivo*. So while the theory may have some rational appeal, the experimental support is tenuous.

Zinkernagel expresses an even more fundamental concern about the basis of this type of research:

> It is particularly difficult to evaluate the relevance of B cell and T helper cell memory, compared to cytotoxic T cell memory and the role of antigen persistence, under conditions where their respective importance in protection from disease or death is usually unknown or not yet clear. (Zinkernagel et al 1996)

The problems encountered with this research carry implications for immunisation. The entire purpose of the procedure of immunisation is to produce a long-term memory response. If this research is accurate, then the vaccine needs to be formulated so that the antigen will end up sequestered on follicular dendritic cells. For vaccines using live, attenuated pathogens this is, perhaps, not such a concern because they are capable of giving a "danger signal" and are processed using the body's normal procedures, whatever they may be. However, for killed, peptide and recombinant vaccines it is important "to establish the length of time that non-viable antigens remain in lymphoid tissues" (Gray & Skarvall 1988, p 72) because these inactivated pathogens or fragments of pathogens may not be processed or

maintained in the body in the same way as viable or live pathogens. This is important not only in formulating the vaccines, but also for designing repeat immunisation schedules. These problems are further highlighted by studies that suggest that memory does not require the persistence of antigen (Wodarz, May & Nowak 2000).

6.4.2 EVIDENCE THAT MEMORY DOES NOT REQUIRE THE PERSISTENCE OF ANTIGEN

There exists experimental evidence that some forms of long-term memory may not require the persistent presence of antigen. Müllbacher found, with reference to cytotoxic T cells, that:

> No statistically significant elevation of lytic activity could be observed when memory T cells were transferred into memory recipients, thus arguing against the notion of a sequestered reservoir of antigen required for the continuous stimulation of antigen-specific T cells to maintain memory. (1994, p 319)

There were various differences in experimental procedure between his experiment and that of Gray & Matzinger, including that Müllbacher transferred five times the quantity of T cells into the recipient mice as was used by Gray & Matzinger. Overall, however, Müllbacher found the differences in their results “difficult to explain” (1994, p 320) which would tend to suggest that there are other parameters influencing long-term immunological memory that have not yet been fully examined.

This view is supported by Hou et al (1994), who observe that:

> Prolonged T cell memory is found for viruses that are unlikely to be re-encountered and which do not persist in the host genome, indicating that [cytotoxic] T cell memory might be independent of continued (or sporadic) antigenic exposure. (p 652)

They performed experiments similar to that of Gray & Matzinger, but they used an "inducing" viral antigen to increase the production of T cell clones, thus making "memory easier to detect in the longer term" (p 652). They concluded that:

> The evidence suggests that the continued presence of viral peptide is not mandatory in mice that have recovered from an acute virus infection. It remains an open question whether vaccines developed to promote antigen persistence will increase [cytotoxic T cell memory] and diminish response time. (p 654)

A similar comment with respect to vaccines is made by Lau et al, who report results that challenge "the current model . . . that long-term memory is dependant on persistent antigenic stimulation" (1994, p 648). They claim that:

> Antigen is not essential for the maintenance of . . . T-cell memory . . . T lymphocytes persist indefinitely in the absence of priming antigen, retain the memory phenotype, . . . and provide protection against virus challenge. These findings suggest a re-evaluation of our current thinking on mechanisms involved in maintaining immunity and have implications towards designing effective vaccination strategies. (p 648)

Neither of these papers explores the nature of the implications for vaccines, however, it means that for vaccines designed to function in this manner, the theoretical basis that underpins their development is uncertain. This is relevant, for example, to vaccines that rely on the use of adjuvants to create long-lasting antigen depots, such as the DTP vaccine, thus casting even further doubts on the validity of the "adjuvant depot effect" as discussed in Section 4.2.3. It also applies to new vaccine technologies such as polymer microspheres (Section 4.5.1.2) and "Trojan horse" viruses (Section 4.5.3.4).

6.5 OTHER THEORIES

6.5.1 A COMBINATION OF LONG LIVED CELLS AND PERSISTENT ANTIGEN

Some researchers hold that a satisfactory explanation involves a combination of long-lived cells and persistent antigen. For Slifka & Ahmed (1998) the rationale behind this is that:

> Although antigen may persist in the form of immune complexes on the surface of follicular dendritic cells for months or longer, it is difficult to understand how antigen may persist in an immunogenic form for decades. An alternative mechanism that is not exclusive to the persisting antigen theory, is that plasma cells may actually live longer than a few days. (p 111)

They cite other studies (such as those by Ho et al 1986; Miller 1964;Okadaira & Ishizaka 1981) that support their own findings to suggest that this is possible. While acknowledging that "the factors involved with sustaining long-term antibody production are still open to debate" (p 111), they suggest the following model for the maintenance of long-term memory:

> During the early stages of a humoral response, large quantities of antigen induce a high degree of stimulation and proliferation. As antigen levels decline, the amount of stimulation and proliferation also decline but antibody levels are still maintained by a long-lived population of plasma cells. Later (ie > 10 years), little to no specific antigenic stimulation exists and antibody production wanes as a function of the number of plasma cells remaining. (Slifka & Ahmed 1998, p 111)

This theory therefore combines the use of persistent antigen and long-lived cells. It has the benefit of offering an explanation not only of how immunological memory may persist for years, or even decades, but also of how it may gradually wane and then disappear over this time. The persistent antigen maintains the stimulation of the long-lived plasma cells, and as this store of antigen declines, so does the population of long-lived cells. However, that these cells are long-lived provides an explanation for the gradual decline in long-term memory.

This view is supported by Swain et al (1996) who assert that:

> Since effective memory can often persist for the lifetime of an animal, often in the apparent absence of a source of . . . Ag [antigen], it seems likely that other mechanisms besides circulating Ab [antibody], must play a major protective role. Indeed it is clear that an increased frequency of T and B cells specific for Ag, are maintained as small resting cells for years or decades after initial immunization. (p 144)

Their study examined the movement of memory cells throughout the body as a whole, not just the lymphatic system, and the role of cytokines on the production of memory cells. They noticed that:

> Transfer of effectors [T cells] to adoptive hosts, without Ag [antigen], leads to development of a population of resting memory cells. (Swain et al 1996, p 162)

The lack of involvement of antigen here is seen as “paradoxical” because it means that there is little opportunity for the development of specific T cell clones. They note that a small number of memory cells circulate throughout the body. Various aspects of this migration, such as capacity for migration, recirculation, and sensitivity to stimulation by antigen are governed or influenced by cytokines. They found evidence that different cytokine patterns (Th1, Th2 or even Th0) influence important factors such as apoptosis, or the rate of death, for different types of cells. They can either stimulate or retard apoptosis, and this can influence the rate of expansion of various effector cells.

> We have yet to directly study memory populations or memory effectors for the status of cell death. . . We also hypothesize that changes resulting in lack of susceptibility to both unstimulated and Ag [antigen]-driven cell death are important characteristics that contribute to the longevity of memory cells and that the regulation of cell death is a critical element in the regulation of the size and duration of the immune response. (Swain et al 1996, p 157)

Factors affecting cell death, longevity of memory cells, and the regulation of the size and duration of an immune response are all vital to successful immunisation. In the time since the publication of the paper by Swain et al in 1996, these issues have still not been clearly or specifically discussed in the scientific literature

available through databases such as Medline and The Web of Science, including Science Citation Index. Consideration of issues such as these have led Swain et al to conclude that:

> Perhaps there is more than one pathway to memory generation . . . Clearly a lot more needs to be done to clearly identify the changes that occur . . . Many key questions remain to be resolved. (p 162)

6.5.2. LONG-LIVED PLASMA CELLS

Slifka et al (1998) examine an alternative pathway to memory generation. They look at the role of long-lived plasma cells. Although they find it plausible that immunological memory may be maintained by the continuous stimulation of memory B cells by persistent antigen maintained on the surface of follicular dendritic cells, this would require a high rate of B cell proliferation and differentiation into plasma cells. They find it hard to understand how the antigen could be maintained for so long without being consumed. Slifka et al (1998) perceive the main problem with this theory is that it is based on the presumption of short-lived plasma cells.

Plasma cells differ in function from memory T or B cells. B cells need appropriate stimulation from T helper cells before they can proliferate and differentiate into antibody secreting cells, whereas plasma cells do not divide and “are unlikely to participate in antigen processing and presentation” (p 363). Plasma cells produce “the majority of serum antibody” (p 363), and continuous secretion of “large quantities of specific antibody” (p 363) is their primary function. They therefore play a significant part in immunological memory because it is important to have specific antibody present in the serum or on mucosal surfaces to deal with subsequent exposure to a pathogen.

> The mechanisms underlying long-term antibody production are not fully understood, but the conventional model postulates that the maintenance of serum antibody requires the continuous proliferation and differentiation of memory B cells into antibody-secreting plasma cells. This model is based

> on the belief that plasma cells are short-lived. . . current immunological dogma holds that plasma cells have a half-life of only a few days. (p 363)

However, these studies all focused on the acute phase of an infection (the first two weeks after the mice were vaccinated), when plasma migrate in response to the infection, and are indeed short lived. After the acute phase of an infection, that is two months to over a year later, the plasma cells in the spleen showed life spans of over a year, and it is postulated that

> . . . at least a subpopulation of plasma cells can survive and continue to secrete antibody for the natural life-span of the immune host. (p 367)

Slifka et al (1998) put forward the convincing argument that this variation in life-span makes sense in terms providing an effective long-term memory response. Early in an infection with a new pathogen, the antibody secreted lacks specificity. Specificity is gradually obtained by the proliferation and selection of the most appropriate clones. It is these specific clones that the body needs to maintain, to provide defence on subsequent exposure. Therefore, effective long-term protection is provided if the early non-specific clones are short-lived, and the later more specific and therefore more effective ones are long-lived and remain to provide long-term protection against subsequent exposure. However, more recently Sze et al (2000) have cast doubts on this argument by providing evidence that:

> . . . early plasma cell death relates to a finite capacity of the spleen to sustain plasma cells rather than a life span endowed by the cell's origin or the quality of antibody it produces. (p 813)

Of the long-lived plasma cells, they assert that only a proportion showed evidence of changing to provide increased specificity of response. They did not, however, dispute that some plasma cells are long-lived, and this now seems to be generally accepted (Manz et al 1998). However, it must be kept in mind that all these

experiments have been done on mice, and the assertion that at least some plasma cells "can survive and continue to secrete antibody for the natural life-span of the immune host" (Slifka et al 1998, p 367) is made in reference to mice. "It remains to be seen" (p 367) whether these findings can be extrapolated in any way to the life-span of plasma cells in humans.

Leyendeckers et al (1999) also provide support for the existence of long-lived plasma cells, however they find that there is no correlation between antibody-based immunity "as determined by measuring serum immunoglobulin titers against a particular antigen" (p 1406) and memory B cell immunity "as determined by counting circulating memory B cells with specificity for that same antigen" (p 1406). This leads them to the conclusion that:

> This lack of a statistically significant linear correlation is in accordance with the idea that B memory cells and plasma cells represent independently controlled forms of immunological memory. (p 1406)

Swain et al (1996) hypothesized that there may be "more than one pathway to memory generation" (p 162) and this result would tend to support this view. The lack of understanding of the function, role and mechanism of these pathways serves as a further indicator of the complexity of the area of immunological memory, and how much is yet to be clarified.

6.5.3 NO MEANS TO MEASURE MEMORY

An entirely different issue is raised by Mitchison (1992). Although he comfortably discusses the phenomenon of immunological memory, he observes that there is no accurate means of measuring it. Cell surface markers are "all that is available for studies in humans" (p 4) and after examining various experimental results he concludes that "there are no markers of memory, but only markers of activation" (p 5). This is supported by Gray who comments that:

> A view proposed by myself and others is that if memory were a function of continued stimulation rather than specialized cells then the 'memory marker' would turn out to be a red-herring. (1993, p 50)

However, if there only exist markers of activation, another problem arises. There are so many candidate cell surface molecules and their response patterns are so varied, it is difficult to know which ones are appropriate indicators. This means:

> We cannot be sure whether the cells we are measuring are activated T cells, effector T cells, or memory T cells. Indeed we do not know if these are various manifestations of the same cell at different points in an antigen-driven cycle of stimulation. (Gray 1993, p 62)

Mitchison echoes this in his description of the process of acquiring memory:

> What happens during immunization is that regulatory T cells become activated, acquire [cell surface markers], proliferate, and become hyperreactive to antigen (the detailed kinetics of these four processes have still to be worked out). After a more or less brief phase of this sort, the stimulated cells revert to a resting phase and lose the markers, but remain present in expanded number. (1992 p 5)

Mitchison also makes the point that *in vitro* assays mainly pick up the period of hyperreactivity, whilst *in vivo* assays may pick up both the hyperreactivity and the expanded cell numbers. This has complicated the interpretation and comparison of experimental results and "raises the question of which of the components mediates protective immunity against infection in humans". As a "reasonable guess" (p 5) he tends to a view similar to that expressed by Slifka et al (1998; see Section 6.5.2.) whereby early proliferation is important as an initial response, and specificity is more important in the long-term. He calls for further experimental investigation on the issue.

6.6 NERVE GROWTH FACTOR

In dealing with the complex minutiae of the immune system, it is easy to lose sight of areas where the immune system interacts with the other complex biological systems of the body. The homeostasis perspectives of theorists such as Cunliffe and Dembic (see Sections 3.5.2 and 3.5.3) are valuable reminders of the

importance of maintaining an awareness of the relationship of the immune system to the body as a whole. In the area of immunological memory, Fuchs (1996) provides a useful reminder of points of comparison between the immune and the nervous systems, and of the existence of areas of interaction between them. He observes that

> . . . both systems comprise a complicated network of cells that are ultimately responsible for defending the vertebrate organism against threats to survival.
>
> The systems must be able to discriminate friend from foe, and in so doing must retain a memory of each dangerous encounter so as to respond more effectively in the future to the same stimulus. Given these similarities, it is somewhat disappointing that immunologists and neurobiologists do not interact more frequently. (1996, p 743)

His focus of interest is Nerve Growth Factor (NGF), a protein which plays an important role in the survival of neurons. It has been shown to influence a variety of cells in the immune system including B cells and T cells, and particularly memory B cells (Aloe, Simone & Properzi 1999; Fuchs 1996).

For memory B cells there is evidence that NGF not only plays a role in their survival, but also has a crucial influence on their ability to function effectively.

> In the absence of NGF, B cells cannot remember the antigens that they have encountered. (Fuchs 1996, p 744)

If this is the case, NGF plays a crucial role in the development of immunological memory. Fuchs discusses possible ways that NGF may participate in the development and maintenance of immunological memory. If it is true that NGF can maintain the survival of memory cells, then theoretically there is no need for cells to continuously proliferate to maintain memory, and thus there is no need to maintain a supply of persisting antigen to stimulate the production of appropriate memory cell clones. Unfortunately there also exists the option that the production of NGF is

induced by the antigenic stimulation of B cells, so contemplation on the role played by NGF only raises new options and does not clarify the issues related to memory and persisting antigen.

The issue is further complicated by more recent findings that T cells also produce and respond to NGF, and this is particularly the case with the Th2 type cells that are involved in inflammatory and allergic responses. This helps to explain the observation of increased levels of NGF in association with such diseases as: asthma (Aloe, Simone & Properzi 1999; Bonini et al 1999; Braun et al 1998), multiple sclerosis (Olson 1998), stress-related disorders (Aloe et al 1997), arthritis and lupus (Aloe & Tuveri 1997). NGF is also present in elevated levels in the acute phase of diseases with inflammatory conditions (Scully & Otten 1995). Possible roles are thought to include acting as an alerting signal in response to threat or stress by stimulating effector T cells, hence the importance of its links with the nervous system (Aloe et al 1997; Braun et al 1998).

The association of elevated levels of NGF with autoimmune diseases has led to cautions regarding its therapeutic use (Fuchs 1996; Scully & Otten 1995). It would appear that a correct level of NGF is essential for effective functioning of the immune system. Too little may damage memory capability and too much is associated with autoimmune diseases. The role of NGF may provide a link between immunisation and claims of resulting allergic conditions and autoimmune diseases (Holt et al 1992; Shoenfeld & Aron-Maor 2000). This will be discussed in more detail in Chapter 7. It is therefore surprising that the role of NGF has not been more extensively studied with respect to immunological memory and the generation of effective immune responses to vaccines.

6.6.1 EXPERIMENTAL CONSIDERATIONS

All the experiments cited in this chapter in relation to immunological memory were

performed on mice in “clean animal facilities” (Gray & Matzinger 1991, p 973). In reality there may be varying levels of re-exposure to the same or a cross-reacting antigen that may play a part in the maintenance of memory. The experiments are also performed either *in vitro*, or on mice with “heavily engineered” immune systems (Benoist & Mathis 1997, p 2000). It is therefore a matter of considerable conjecture to what extent these findings can be extrapolated to the human immune system.

6.7 CONCLUSION

The study of immunological memory is one of the more uncertain areas of immunology. The definition of memory, and appropriate parameters by which to measure it, are surrounded by considerable confusion. Experimental results often raise more questions than they answer, and several different theories, such as persistent antigen, long-lived clones and long-lived plasma cells, all have good experimental support and all seem feasible. However, the development and maintenance of immunological memory is the primary purpose of immunisation. Current understanding of the function of licensed vaccines, and the creation of new vaccines, would be substantially enhanced if the details of immunological memory were better understood.

SECTION TWO: IMMUNISATION AND EFFICACY

CHAPTER 7

UNINTENDED LONGER-TERM CONSEQUENCES OF IMMUNISATION

7.1 INTRODUCTION

The aim of immunisation, according to Roitt (1998), is to elicit a response from the immune system to a particular antigen that will lead to the development of immunological memory (presuming such a thing exists, see Chapter 6). It is attractive to think of this as a simple causal relationship, and often it is researched and discussed as though it is. However, the preceding chapters should have made clear that few things in immunology are simple or straightforward, and immunological responses to immunisation are no exception.

Ideally a vaccine will provoke an antibody response, but the production of this response involves a complex and incompletely understood set of cellular and

chemical interactions that affects the immune system as a whole, and possibly other biological systems in the body (see sections 3.5.2 and 3.5.3). It is a process that varies according to the nature of the pathogen, and will often elicit in the body the same physical responses that accompany a natural infection, such as fever and inflammation.

Public concern over possible adverse effects of vaccines has led to an almost paradoxical tendency to pursue the development of vaccines that elicit an effective antibody response from the immune system, but at the same time have few if any physical manifestations associated with this response. In an appropriately instructed public, mild to moderate responses associated with an infection are not generally a cause for concern. They are in fact often welcomed as a sign that the immunisation has been effective (Gershon 1991). Mild to moderate responses include: swelling and redness at the injection site, irritability, fever below 40°C or a degree of “malaise” lasting one or two days (CSL 1997; Lederle 1993; NHMRC 2000a; SmithKline Beecham 1997.)

Mothers report feeling concerned when (Kilmartin et al 1998) they perceive that health professionals do not give significant recognition to, or attempt to dismiss, a child’s response to immunisation that parents consider to be severe or not normally associated with a moderate infection. This may include responses such as convulsions, prolonged crying, high pitched screaming or extensive swelling at the injection site (see Section 7.2). One reason for this concern is that these severe or unusual reactions indicate to parents a possible systemic (general) reaction with broader and longer-term implications. When parents are told that these severe reactions are “normal” and are made to feel as though they are overreacting, they often comment that the doctors’ assertions are counter-intuitive (see for example AVN 1998, pp 85, 113, 121,138,139). It has been observed in many instances that

mothers have a better perception of the epidemiological reality of immunisation practices than medical practitioners (Aaby 1995).

It is therefore worth examining childhood immunisation as a potential causal factor in the development of longer-term systemic conditions involving the immune system and possible connections between severe systemic or local reactions and the development of these conditions. However,

> . . . although assessment of the rates of common medical events following immunizations, such as local tenderness or fever, has been easily achieved in small pre-licensure studies, assessment of the rate of occurrence of less common medical events, such as seizures or neurological damage, has been limited by the small size of vaccinated populations in pre-licensure studies. After licensure, assessment of the rates of medical events has relied on other methodologies, including active reporting of medical events or the performance of case-control studies. *Neither of these methodologies allows accurate assessment of the rates of medical events. Both may fail to identify medical events not known to be associated with immunization.* (Black et al 1991, p 364, italics mine.)

Further to this, when it is suggested that there may be a link with a longer-term condition, any substantiating evidence is usually met with considerable resistance from the medical, research or government authorities with an interest in the promotion of immunisation. This has been exemplified in the debates over a link between the MMR vaccine and autism and/or irritable bowel syndrome (see Elliman & Bedford 2001; Peltola et al 1998; Wakefield & Montgomery 2000; Wakefield et al 1998) and Hib vaccine and type 1 diabetes (see Classen & Classen 1999; Karvonen, Cepaitis & Tuomilehto 1999)

There are many problems in conducting and analyzing epidemiological studies into longer-term consequences of any type of medical intervention. The difficulties include:

- Ascertaining and defining cases of the various conditions, especially if they are uncommon.

- Identifying and examining a sufficiently large population base to provide meaningful statistical data.
- Finding qualifying cases. This is easier if they require hospitalisation, but presents difficulties if they are only on the records of private physicians and do not require mandatory reporting.
- For some conditions few or no previous studies have been done, thus making it difficult to ascertain trends in prevalence.
- There are difficulties in making comparisons between studies that have used different criteria for selection or statistical analysis.

(from Jacobson et al 1997)

These issues will be examined in more detail in Chapter 9. This chapter will examine the possible association between severe local and systemic reactions to immunisation and the development of longer-term conditions such as atopy (allergic conditions) and autoimmunity.

7.2 SHORT-TERM LOCAL AND SYSTEMIC REACTIONS

Local reactions to vaccination are those that are confined to the area around the innoculation site. Systemic reactions involve one or more biological systems in the body, and in the case of immunisation this is primarily the immune system, but sometimes others such as the nervous system are also involved.

7.2.1 LOCAL REACTIONS

Local reactions to immunisation mostly involve swelling and redness at the injection site that resolve over a couple of days. The prevalence varies between vaccines, for example this reaction is observed in about 50% of children given DTP whole cell vaccine, and about 5% of those given Hib vaccine (NHMRC 1997, p 43).

There is evidence that the frequency and degree of local reaction may be influenced not just by the composition of the vaccine and the reactive propensity of the child's immune system, but also by technical aspects of administration. The

length of needle used for injection has been shown to be a significant factor contributing to the experience of local reactions. Longer needle length (25mm compared to 16mm) has been shown to significantly reduce rates of local reactions in children presenting for their third DTP vaccination (Diggle & Deeks 2000). This study does not quantify the degree of local reaction, only the duration, nor was there any scope for comparing the study results of the reaction to the first two doses of DTP in individuals. Variations in needle gauge do not appear to be such an influential factor (Mark, Carlsson & Granstrom 1999). The reason for these findings is thought by Diggle & Deeks (2000) to be that the longer needle length ensures that the vaccine is injected well into the thigh muscle, particularly in infants a few months old.

Local reactions to injected substances are usually “self-limiting”, that is they resolve without treatment. They occur not only in response to an injected antigen, but to other substances as well. Even unaccompanied adjuvants can produce swelling and redness on injection (Cox & Coulter 1997; Relyveld, Bizzini & Gupta 1996). These responses are usually minor and not perceived as a cause of concern by medical practitioners, or by parents who are adequately informed (AVN 1998; NHMRC 1997).

Occasionally local reactions may be more severe, and while medical practitioners may still not see this as a cause for concern, parents may do so. Here is the description of varying degrees of local reactions provided by the DTP product insert, followed by two brief reports of parental experiences of these reactions. Note the contrast between the detached, technical language of the product insert and the parents’ descriptions of their personal experience of these reactions.

DTP product insert

> Mild to moderate - a nodule may be palpable at the injection site for a few weeks. Abscess formation at the injection site has been reported occasionally. Severe - an extensive area of redness and swelling which becomes indurated and involves most of the antero-lateral surface of the thigh or a major part of the circumference of the upper arm. This reaction may increase in severity with each subsequent injection. (CSL 1997)

Adverse parental reports

> After my son Jamie's second DTP shot he had a hard red and painful lump, about the size of a golf ball, on his bottom at the injection site. . . I was told this was a normal reaction. (McLennan 1998, p 117)

> Her thigh had a lump the size of a 20c piece [approximately 3 cm] at the injection site for nearly 6 weeks. I was assured that Hannah's reactions [including prolonged high fever] were quite normal . . . and was made to feel that I was over reacting. (Anonymous 1998, p 113)

Each of these children went on to develop more serious systemic reactions. In Jamie's case they were neurological, and in Hannah's case they were atopic. There is a suggestion here, and from other similar reports (AVN 1998), that a severe local reaction may be predictive of a more serious longer-term effect (see Section 7.6.2). However this has not been well studied, as a thorough search through both Medline and The Web of Science produced no relevant references.

7.2.2 SYSTEMIC REACTIONS

Mild systemic reactions to immunisation include fever <40°, irritability and "malaise" for one to two days post-immunisation. Severe reactions include:

> Anaphylaxis, bronchospasm, larygeal odema [swelling of the throat], generalized collapse, prolonged unresponsiveness (hypotonic/hyporesponsive episode) convulsions, prolonged inconsolable screaming, encephalopathy, thrombocytopaenia. (CSL 1997)

These types of reactions have been researched by vaccine manufacturing companies and vaccine researchers, in relation to their causal connection to immunisation. The results, although indicative of a causal connection, are disputed on the grounds that the temporal connection may be coincidental (CSL 1997;

NHMRC 1997). They have not, however, been researched as an indicator of resultant longer-term conditions.

7.3 TYPES OF LONGER-TERM REACTIONS

There is evidence that some vaccines may have beneficial effects on the immune system that are broad-ranging and unquantified. This is particularly the case with measles vaccine (Aaby 1995) and a similar claim has been made for the BCG vaccine (Marchant et al 1999). However, less desirable longer-term effects have also been associated with immunisation. These include the development of atopic and autoimmune conditions.

7.4 BENEFICIAL EFFECTS

The most obvious beneficial effect of successful immunisation occurs when it fulfills its purpose and produces an enhanced memory response on subsequent exposure to a pathogen. Most vaccines are only evaluated in respect to their efficacy in protecting from the particular pathogen for which they are designed. This efficacy is usually evaluated simply in terms of serum IgG antibody levels for that particular pathogen, although there is debate as to the validity of this as an accurate measure (see Sections 2.9.2, 2.9.5, 3.8). It is only occasionally that the wider effects of any immunisation program are examined.

Only a few studies have looked at the wider effects of immunisation in respect to issues such as the disease rates in immunisation exemptors (eg Feikin et al 2000; Gangarosa et al 1998), or the simultaneous administration of multiple vaccines (Midthun, Horne & Goldenthal 1998; Powell 1996).The most comprehensive study has been done with measles vaccine. This is primarily due to the considerable volume of research produced by Aaby and colleagues in Guinea-Bissau. They have

provided broader discussions of the relationship of their findings to measles immunisation research world-wide (for a relevant selection of this considerable body of work see: Aaby 1995, Aaby et al 1986; 1987; 1988a; 1988b; 1990a; 1990b; 1992; 1995; 1996; Lisse et al 1998; Shaheen et al 1996).

Aaby's research on factors as diverse as nutritional status (Aaby et al 1996), time and source of exposure to measles virus (Garenne & Aaby 1990), and gender (Aaby & Molbak 1990), have led to a re-examination of some of the assumptions underlying the scheduling and promotion of immunisation (Aaby 1995).

> Evaluations of immunization programmes are usually based on the assumption that vaccines have an impact only against specific diseases. This assumption may not be correct for measles vaccine. Recent studies indicate that vaccines may have important non-specific effects . . . (Aaby et al 1995, p 481)

This initially came to light with the reduced long-term survival of children who received the high-titre Edmonston-Zagreb measles vaccine, compared with children who received the standard titre vaccine (Aaby et al 1988b).

> There were many peculiar aspects to this. One of them was that it was gender specific – it happened more in the girls. Secondly, the increased mortality was due to death from a total miscellany of causes; certainly not specifically deaths from measles. (Nossal in Brock & Goode 1997, p 143)

However, for children who received the standard titre vaccine, studies have reported "a greater than expected reduction in mortality in areas with high mortality" (Aaby 1995, p 481) that was not due solely to the prevention of death from acute measles and its specific sequelae. These findings are in accordance with other studies that suggest that lower antigen doses are often more effective (see Sections 5.2.1; 5.3.1; 5.3.2).

There was no similar reduction in mortality found for DTP or polio vaccines. In fact these vaccines were associated with a slightly increased mortality (Aaby 1995).

> The simplest explanation would seem to be that measles vaccine activates the immune system in a non-specific way providing protection against other infections. (Aaby 1995, p 484)

It has also been observed that measles infection in childhood, as well as measles immunisation, prevents the development of atopy, or allergic conditions (Shaheen et al 1996). A similar claim has been made for BCG vaccine. There is evidence that it influences the immune system of the newborn to develop a Th1 type response (for detailed discussion of Th1 and Th2 responses, see Sections 2.6; 4.2.1 and 5.3). This aids their ability to respond to diseases caused by mycobacteria and viruses, and also reduces the prevalence of the Th2 type response that is associated with the development of atopic reactions (Marchant et al 1999). This will be discussed in detail in Section 7.5.

The evidence that a vaccine can have beneficial effect that goes beyond just providing protection for the specific disease for which it is designed, raises several issues for immunisation, including:

- The need to reevaluate effects of the timing and number of doses of other vaccines.
- The need to evaluate new vaccines in terms of their effect on survival before their introduction.
- The need to continue immunisation even after eradication of measles to maintain the same beneficial effects, unless some other means to achieve this was identified (see Zinkernagel 1998).
  (from Aaby et al 1995)
- The need to examine all current paediatric vaccines in the light of these findings, especially as there appears to be a variation in the type of long-term effect.

7.5 ATOPY

7.5.1 INCREASING PREVALENCE OF ATOPY

Atopy is defined as

> . . . a state of allergic response, mediated by IgE, to largely innocuous, common environmental antigens . . . it underlies the clinical diseases of asthma, hay fever, and eczema. (Shirakawa et al 1997, p 77)

Statistics from many studies demonstrate that the prevalence and severity of atopy and associated allergic diseases has risen world-wide in the last few decades (see for example, Burney, Chinn & Rona 1990; Burr et al 1989; Chadwick & Cardew 1997; Cookson & Moffatt 1997; Prescott et al 1999; Shaheen et al 1995; Taylor et al 1984). Increases have even been recorded in areas such as Africa and Asia where atopic diseases like asthma were previously rare. In North America and Europe, allergic diseases currently affect more than 15% of children and adults (Plaut, Dickler & Rotrosen 1998).

It is necessary to be mindful that some of the apparent statistical increases may be due to external factors that influence recording methods. These may include detection bias as a result of increased publicity and awareness of the conditions, and changes in diagnostic criteria. There are also difficulties in drawing conclusions about long-term trends when extensive data has only been available in many areas for a decade or so (Chadwick & Cardew 1997).

However, the currently available data suggest that atopic conditions are increasing world-wide, notably in children and young adults. For example studies have shown that asthma diagnosis for 8-11 year olds in Australia increased from 12.9% in 1982 to 29.7% in 1992. In Scotland, for 8-13 year olds it increased from 4.1% to 19.6% between 1964 and 1994. For Taiwan the figure for current asthma in 7-15 year olds

has risen from 1.3% in 1974 to 10.8% in 1994 (In Woolcock & Peat 1997, p 123).

So far the environmental changes that have been suggested as contributing to this rise in atopy include:

- air pollution.
- increased environmental toxins such as pesticides, herbicides and fungicides.
- increased indoor exposure to dust mite antigens.
- dietary changes.

(Henderson et al 1999, Shirakawa et al 1997).

There is also concern expressed by some parents (Australian Vaccination Network 1997; James 1988, p 11-19; Taycare 1997), health professionals (Blomfield 1998; Golden 1997, p 11; Kalokerinos 1974, p 59; Mendelsohn 1984; Rose 1997; Sinclair 1992, p 40-43; Smith 1994; Taycare 1997) and scientists (Henderson et al 1999; Kemp et al 1997; Odelram et al 1994; Odent, Culpin & Kimmel 1994; Rook & Zumla 1997) that immunisation may be a contributing factor. Its widespread use, accompanied by the decline of many infectious diseases in Western countries, is certainly temporally associated with the rise in atopy.

While it has been shown that some vaccines, such as measles and BCG may have long-term benefits and help prevent the development of atopic conditions, other vaccines, particularly DTP, have been associated with the exacerbation of atopic conditions. So also has the practice of administering multiple vaccines at the one time (Rook & Zumla 1997; Shoenfeld, Aharon-Maor & Sherer 2000). This will be discussed in detail in Sections 7.5.3.

Statistics (as reported in Chadwick & Cardew 1997; Peat et al 1994) show that allergic respiratory diseases, and particularly atopic asthma have increased progressively since the early 1960's. This is synchronistic with the introduction of widespread mass immunisation of children for pertussis, diphtheria and polio was

widely implemented during the 1950's. Measles immunisation was introduced during the 1960's.

There is evidence that childhood infections play a part in the development of the immune system, by "either mobilizing general defense mechanisms or 'teaching' a lesson in how to handle other infections" (Aaby 1995, p 683) and that their immunisation-induced decline means this developmental role may now be lacking (Cookson & Moffatt 1997; Kramer 1999; Shaheen 1996; Shirakawa et al 1997; Strachan, Taylor & Carpenter 1996). It is possible that the link may be stronger. The actual process of immunisation may be directly causative, or at least a triggering mechanism in the development of atopy in some children.

7.5.2 EVIDENCE OF CONCERN ABOUT A POSSIBLE LINK BETWEEN IMMUNISATION AND ATOPY

7.5.2.1 Comments from parents:

These comments are from parents who have been motivated to write detailed accounts of their experiences of immunising their children for publication by the Australian Vaccination Network (AVN). These, and other accounts in the book *Vaccination Roulette* (AVN 1998) have two common themes. They express a concern about the perceived effects of immunisation on the health of their children, and dissatisfaction with the response of their local immunisation providers, particularly their failure to acknowledge their concerns and provide of adequate relevant information.

> There are many other children and babies in this area that are suffering similar reactions [asthma and eczema] and we are all being told that it is purely coincidental. (Hawkins 1998, p 140)

> Fourteen days [after her second DTP shot], our baby developed eczema . . . She also began to have ear drainage problems and later

> developed numerous food allergies, with one doctor describing the quantity of these as ‘over the top’. (Klotz 1998, p 157)
>
> I [was] told . . . that he had to have his vaccinations, so I dutifully took him to the doctor and had it done. Not a thought entered my head to ask a question about the procedure and indeed not a word was ever mentioned about adverse reactions or anything. (Messenger 1998, p 88)

7.5.2.2 Comments from health practitioners:

These comments reflect the experiences of a variety of health practitioners: a general practitioner, a nurse and a paediatrician. Although the official stance of their professions is that vaccines are safe and effective, these individuals are representative of a section of health professionals who have expressed concern about unrecognised and long term effects. Speaking out publicly against immunisation as a medical practitioner carries with it the threat (Cosford in Taycare 1997), and sometimes the reality (McFarlane 1995) of being “debarred” from the profession. These quotes have been obtained from the publications and videos of natural health practitioners or immunisation information awareness groups such as the Australian Vaccination Network.

> Many parents report that their children become increasingly intolerant of certain foods after vaccination. Griffin - medical practitioner, PhD. (1998, p 97)
>
> I find a lot of people who had a problem with pertussis vaccine when they were children. They end up with a lot of respiratory problems. They get the sinus, the chest problems, the glue-ear . . . Rose - nurse specialising in allergies (In Taycare 1997)
>
> There may be a relationship between immunization as a stress and the onset of some of the devastating array of [atopic] symptoms I am seeing all the time in younger and younger children. Paediatrician (In Sinclair 1992, p 41)

(See also AVN, 1998. pp 59, 85, 115, 188, 306; Taycare 1997, and more detailed discussion in Chapter 14of this thesis.)

7.5.2.3 Comments from scientific journals:

Scientific studies on the association between atopy and childhood immunisation have provided confusing results. Pertussis is the main vaccine that has been studied in relation to atopic conditions, and some studies do show a link (Kemp et al 1997 [cohort study]; Odent, Culpin & Kimmel 1994 [population-based cross-sectional study]; Odelram et al 1994 [randomised double-blind control trial]; Schuster, Hoffman & Reinhardt 1993 [prospective study]), while others don't (Butler et al 1982 [longitudinal cohort study]; Nilsson et al 1996 [randomised double-blind control trial]; Wjst et al 1994 [population-based cross-sectional study]). An important point to note here is that some studies examined pertussis vaccines only, while other studies used the combination DTP vaccine, so direct comparisons are difficult. However, there is evidence that the administration of multiple vaccines may be associated with the development of atopic states (see Section 7.5.3; Rook & Zumla 1997; Shoenfeld, Ahron-Maor & Sherer 2000).

The comments below provide a summary of the findings of scientific studies reported in respected journals that show a statistically significant link between immunisation and childhood diagnosis of atopic conditions such as asthma and allergies. They all conclude that the link is significant enough to warrant further investigation.

> . . . in Christchurch, New Zealand, the Wellington Asthma Research Group studied 1265 children aged 10 years and found that none of the 23 children who had not received diphtheria, pertussis, and tetanus or polio immunisations had recorded consultations for asthma or other allergic illnesses whereas 23% of the immunised children had had episodes of asthma and 30% had consultations for other allergic illnesses. [This report and the one by Odent, Culpin & Kimmel 1994] point a strong finger of suspicion at childhood immunisation being the cause of the remarkable increase in childhood asthma and allergies over the past few decades. (Blomfield 1998, p 205; for full report see Kemp et al 1997 [longitudinal study])

> The surprise came when we classified the questionnaire according to pertussis vaccination. Among 243 immunised children . . . 26 were diagnosed as having asthma (10.69%), compared with four (1.97%) of the 203 children . . . who had not been immunised. . . Up to now we have not been able to detect any confounding factors explaining such differences . . . Therefore the focus should be on pertussis. (Odent, Clupin & Kimmel 1994, p 593 [population-based cross-sectional study])

> The correlation between total IgE and PT-IgE [pertussis toxin - immunoglobulin E], which was most prominent in children with atopy, indicates that the role of immunization for the development of allergy merits further studies. (Odelram et al 1994 [randomised double-blind control trial])

7.5.3 MECHANISMS BY WHICH IMMUNISATION MAY INFLUENCE THE DEVELOPMENT OF ATOPIC CONDITIONS

It is only recently that research into the development of the child's immune system has begun to clarify the processes by which atopic states develop and persist in young children. Studies suggest that "the first three years of life may be important for the acquisition of atopy" (Van Asperan, Kemp & Mukhi 1990, in Woolcock & Peat 1997, p 128). These studies have focused primarily on the role of T cells and their associated cytokines. They offer hope that some of the immune imbalances that predispose to atopy may be avoided, or rectified if they arise (Bleeker, Postma & Meyers 1997; Holt et al 1997; Prescott et al 1999; Shirakawa et al 1997; Warner et al 1997). However, to use this research to its full potential, a clear understanding must be gained of the operation of environmental factors on the developing immune system, so that exacerbating conditions can be minimized.

The current understanding of the development of the infant's immune system does make plausible a connection between immunisation and atopy. The key issue is the balance between the two types of T helper cells, Th1 and Th2, and the respective roles they play in different types of immune response (for further discussion of Th1 and Th2 responses, see Sections 2.6; 4.2.1 and 5.3).

> Atopy in adults is associated with the long-term expression of allergen-specific immunity, characterised by production of T-helper 2 (Th2) cytokines such as interleukin-4 and interleukin-5, which promote IgE production and eosinophilia. By contrast, non-atopic people show mainly T-helper 1 (Th1) immunity characterised by production of interferon-γ, which inhibits the growth of Th2 cells. (Prescott 1999, p 196)

Normally a predominance of Th2 type immunity is indication of pathology,

> . . . except during pregnancy, when it develops naturally. This is because control mechanisms . . . limit capacity for intrauterine induction of Th1 responses, especially responses involving interferon-γ, which is highly toxic to the placenta. (Prescott 1999, p 200)

If this shift to a predominately Th2 type of immunity does not occur, then there is an increased risk of miscarriage, but as a consequence, both in the womb and after birth, a child's immunity is predominately Th2 (Björkstén 1999).

Studies have shown that fetal and neonatal T cells have a much lower capacity to produce the Th1 cytokine, interferon-γ, than do adult T cells. The ability to mount an effective Th1 type immune response develops gradually, with production of interferon-γ increasing progressively from birth until about five to seven years (Holt 1995).

The period from birth to six months is a particularly critical time. The ability to rapidly increase the production of interferon-γ in the months after birth is a crucial factor that differentiates non-atopic from atopic children. This is because interferon-γ inhibits the production and maturation of Th2 cells, and if it is not present in sufficient amounts early enough, Th2 memory cells (those able to "remember" an antigen encounter and respond very quickly on subsequent exposure) are able to proliferate. A balance between Th1 and Th2 responses, and

the ability to control Th2 responses when necessary is then very hard to achieve

(Prescott 1999).

> . . . absence of an effective Th2 inhibitory signal at this time may permit early expansion and maturation of Th2 memory cells, such that negative control via competing Th1 cells cannot be readily achieved. (Prescott 1999, p 200)

A study by Holt et al (1992) found evidence that the postnatal development of immune competence is slower in children who are genetically at high risk for atopy. They found a

> . . . markedly reduced frequency of immunocompetent T cell precursors in the blood of high risk children . . . and moreover demonstrated lower production of IL-4 and (particularly) IFN-γ in cloned cells from this group. This finding has been confirmed [by other researchers including Martinez et al 1995 & 1997], . . . indicating that children at greatest risk for development of allergic disease are those with the lowest capacity for IFN-γ production, which may limit the efficiency of Th cell switching to Th1. (Holt et al 1997, p 44)

Identifying children who are genetically at risk of developing atopy is possible, as there is an identified hereditary pattern. Research shows that 50% of children with one allergic parent and 80% of children with two allergic parents become atopic. Also development of atopy is more significantly linked with allergic mothers than with allergic fathers, as it is not only passed on at the chromosomal level, but also by the conditions experienced by the fetus *in utero* (Warner et al 1997, p 221).

Many studies acknowledge the role that microbial exposure and early childhood infections play in aiding the development of a more effective Th1 type immune response (eg Björkstén 1999; Martinez 1994; Prescott 1999; Romagnani 1992; Rook & Stanford 1998; Shaheen 1996; Strachan, Taylor & Carpenter 1996). This is because

> . . . the ‘natural’ immune response to bacterial and viral infections increases

> the production of interferon-γ and interleukin-2 cytokines that selectively enhance the development of Th1-type lymphocytes, and suppress Th2-type differentiation. (Strachan, Taylor & Carpenter 1996, p 422)

To summarise, the current understanding of childhood immunity holds that infants are born with a dominant Th2 type (atopy related) immune profile. In the first six months of life a normal infant should rapidly increase its production of interferon-γ as it develops the ability to mount appropriate mature Th1 type immune responses. This transition continues gradually for the next five to seven years, with the assistance of exposure to various bacterial and viral infections, until an "adult-type" balance between Th1 and Th2 type immunity is achieved. If this transition is not successfully achieved and the child retains a predominately Th2 type profile, it is prone to atopic disease. For a child with a family history of atopy it is likely that this transition, especially in the important initial stages, will be slower and less effective than average.

There is evidence that immunisation influences the Th1/Th2 cytokine balance.

> Vaccinations or infections can exert a long-lasting systemic effect, and non-specifically increase or reduce the Th1 to Th2 cytokine balance of the response to other unrelated antigens. This systemic effect influences survival from unrelated diseases. (Rook & Zumla 1997, p 1831)

DTP induces a Th2 cytokine response, as does the simultaneous administration of multiple vaccines (Rook & Zumla 1997; Shoenfeld, Ahron-Maor & Sherer 2000).

The current paediatric immunisation schedules, in most nations, call for the simultaneous administration of multiple vaccines. It is recommended that at two, four and six months of age, an infant simultaneously receive:

- DTP (Diphtheria, Tetanus, Pertussis)
- Poliomyelitis – 3 strains
- *Haemophilus Influenzae* type B
- Hepatitis B
  (NHMRC 2000a)

This administration of multiple vaccines may influence the natural development of a balance between the initial Th2 and the evolving Th1 types of immunity, particularly in children genetically at risk of atopy for whom this maturation process is slower than average.

7.5.4 TH2 AND THE CHILDHOOD IMMUNISATION SCHEDULE

For reasons that are possibly erroneous, and which have been discussed in sections 5.2 and 5.3, the infant dose of tetanus, pertussis, and polio vaccines is the same as the adult dose, and therefore, in effect, several times the adult dose on a per kilogram basis. For diphtheria it is considerably higher, 30 Lf [limit of flocculation] for infants compared to 2 Lf for adults. This is in contrast to the dose per weight schedule that is usual for nearly all other drugs and supplements. The administration of a higher dose to infants is based on the theory of neonatal tolerance, the validity of which is increasingly being questioned (see Chapter 5).

Simultaneous administration of these doses of DTP, OPV (which carries three strains of attenuated polio virus), Hib and HBV, in an infant, would therefore constitute a considerable antigenic load, particularly as DTP, Hib and HBV are injected, thus bypassing the body's normal defense mechanisms. Even the scheduling at two, four and six months would constitute a concentrated exposure to these antigens. Further to this, the use of aluminium compounds as vaccine adjuvants has been linked with a Th2 profile and increased Ig E responses (see

Section 4.4 and Kovarik & Seigrist 1998), especially in children with atopy (Odelram et al 1994). Aluminium compounds are employed as adjuvants in the DTP, Hib and HBV vaccines.

Significantly, infants are exposed to all these atopy inducing factors at the same time as their developing immune systems are required to significantly increase production of interferon-γ, and make a natural shift from Th2 to Th1 type immunity. Obviously the majority of infants manage this transition to Th1 type immunity despite the immunological obstacles presented, however

> . . . the reduction in Th1 function is much greater in individuals genetically at risk of atopy. (Prescott 1999, p 199)

For infants prone to atopy, who are already at a disadvantage in making the normal Th2 to Th1 shift, the early childhood immunisation program could feasibly be a major contributing factor to the

> . . . persistence of the fetal Th2 responses during early childhood in atopic individuals and subsequent expression of disease. (Prescott 1999, p 196)

Of the adverse reactions to vaccines reported to the Vaccine Adverse Event Reporting System (VAERS) in the United States during 1991-94, 75.7% of the 38,787 reports followed the administration of multiple vaccines (Braun & Ellenberg 1997). The studies done by Odent, Culpin & Kimmel (1994) and Kemp et al (1997) both showed significantly lower rates of asthmatic and atopic conditions in unimmunised children. It is also interesting that several studies on atopy, and particularly on asthma, have noted that the prevalence of allergies and asthma is lower in the younger children of large families than children higher in the birth order, (eg Cookson & Moffatt 1997; von Mutius et al 1997; Shaheen 1996; Shirakawa 1997; Strachan 1989) and this is usually, and feasibly, interpreted as

"indirect evidence that infection early in childhood may prevent allergic disease." (Shaheen 1996) However, it is also recognised that larger family size is associated with lower immunisation rates for the younger children (Forrest, Burgess & McIntyre 2000; Ponsonby et al 1997) simply because the mother often becomes too busy to remain as conscientious about immunisation as she was with the older children. Further studies could usefully examine this link.

7.5.5 SUMMARY OF FINDINGS ON IMMUNISATION AND ATOPY

Infants are born with a predominately Th2 cytokine profile. During the first five to seven years, and particularly in the first six months of life, they develop the Th1 cytokine profile that is an important part of the body's defence against infectious diseases. The maintenance of a predominately Th2 profile has been linked with the development of atopic conditions in both children and adults. The DTP vaccine, the use of aluminium compounds as adjuvants, and the administration of multiple vaccines, have all been shown to cause a dominance of Th2 cytokines, thus inhibiting the development of the Th1 profile in infants.

Feasibly, immunisation may be acting as a causative or triggering factor in the development of atopic states, particularly in those infants genetically prone to the development of atopy. Immunisation may therefore require inclusion in the list of environmental factors considered to be contributing to the significant increase in the rates of childhood asthma and general atopy in the last few decades.

7.6 AUTOIMMUNITY

"The conception that antibodies, which should protect against disease, are also responsible for disease, sounds at first absurd." (von Pirquet in Silverstein 1989, p

214). However, “inappropriate immune responses to self” (Mason, 1992, p 126) do occur, and these constitute the diverse group of autoimmune diseases.

There are several problems with finding accurate epidemiological information on autoimmune diseases. These include:

- Their diversity.
- Lack of consensus on disease definition.
- Dispute over the etiology of many disorders.
- Lack of accurate and easily accessible case histories.
- Lack of epidemiological studies on many disorders.
- Difficulty in comparing epidemiological studies because of different selection criteria, sample sizes, methodologies and statistical analyses.

(from Jacobson et al 1997)

In the last decade there has been increasing attention to the possibility of a link between immunisation procedures and the development of autoimmune conditions, but the results are contradictory, confusing, and subject to much debate (Shoenfeld & Aaron Maor 2000). However, there has been an increase in autoimmune conditions corresponding to the introduction of increasing numbers of vaccines in the paediatric immunisation schedule (Black 2001; Roe 2002), and:

> Even though the data regarding the relation between vaccination and autoimmune disease is conflicting, it seems that some autoimmune phenomena are clearly related to immunisation. (Shoenfeld & Aaron-Maor 2000, p 1)

The following is a list of autoimmune conditions and the vaccines that have been suggested as being implicated in their etiology (from Shoenfeld & Aaron-Maor 2000):

CONDITIONS	VACCINES
Arthritis.	Tetanus, Typhoid, Parathyroid, Polio, Mumps, Diphtheria, Rubella, Smallpox, Parvovirus, Hep B, Hep C, MMR.
Autism. (autoimmunity has been suggested as a contributing factor in this condition)	The measles component of MMR.
Chronic inflammatory bowel syndrome.	MMR.
Diabetes Melitus.	Immunisation in general, but particularly Hib. Some vaccines exert a protective effect.
Gullian-Barre syndrome (GBS).	Tetanus, BCG, Rabies, Smallpox, Mumps, Rubella, Hep B, Diphtheria, Polio, Hep B.
Lupus vulgaris	BCG (especially with repeated doses).
Systemic Lupus Erythematosus (SLE)	Hep B.
Multiple Sclerosis (MS)	Hep B, Measles
Systemic autoimmune disease	Smallpox, Asiatic influenza, Pertussis, Tetanus.
Systemic conditions with renal Symptoms	Polio, Smallpox, Tetanus, Influenza.

7.6.1 CAUSES OF AUTOIMMUNE CONDITIONS

"There is no spontaneously developing autoimmune disease for which the etiology and pathogenisis are understood." (Mason, 1992, p 135) This is primarily because:

> The evolvement of autoimmune diseases is presumed to entail an interplay between several factors, constituting a distinct 'atmosphere' which enables a triggering event to evoke the disease. (George, Levy & Schoenfeld, 1996, p 3)

That is, there is a difference between an autoimmune *state* and autoimmune *disease* (von Herrath & Oldstone 1995). The existence of an autoimmune state refers partly to the fact that individuals who develop autoimmune disease usually have a predisposition to the condition that involves genetic factors, and partly to the

existence of a latent period where the condition is developing and before clinical signs of disease are observed. This is why Schoenfeld & Aaron-Maor (2000) were able to comment on the consistent 2-3 month time lag after immunisation before the report of disease. The shift from having a predisposition to the development of disease during the latent period usually requires a triggering factor. This is often hard to identify because of the time-lag between the triggering factor and the recognition of disease, however there is evidence that triggering factors include stress, major injury or surgery (Elenkov & Chrousos 1999; Winfield & Jarjour 1991), viral infections (Paroli et al 2000, von Herrath & Oldstone 1995) and immunisation (Schoenfeld & Aaron-Maor 2000; Older et al 1999).

7.6.2 THE IMMUNE SYSTEM AND AUTOIMMUNE CONDITIONS

Many components of the immune system have been implicated in the development of autoimmune conditions, and many processes have been proposed to explain its development.

There is evidence that autoimmune reactions may involve the class of molecules known as heat shock proteins (also known as stress proteins). These are the proteins postulated by Matzinger to act as the “danger signal” in her model of the immune system (see Sections 3.4, 3.6, 3.7, 3.8). These molecules are produced both by the pathogen and by the human host during an infection, because both organisms are under stress.

> Increased synthesis and altered expression of extremely similar sets of autologous and foreign molecules occur at a time of active immune response, thereby placing stress proteins uniquely at the interface of tolerance and autoimmunity. (Winfield & Jarjour 1991, p 162)

Heat shock proteins are produced during tissue inflammation. Periods of prolonged inflammation are implicated in the development of autoimmune conditions (Paroli et

al 2000). This is partly because the continued presence of similar self and foreign proteins means that the body may start reacting to the self proteins, and after the resolution of inflammation continues to do so. Matzinger notes that autoimmune reactions are common during the natural healing processes associated with inflammation, but are usually temporary. Autoimmune states develop when they continue and become chronic (Matzinger 2001).

Prolonged tissue inflammation not only allows reaction to self heat shock proteins, but also allows for the:

> Activation of by-stander T cells and the recruitment of memory T cells mediating further tissue injury and the release of additional cryptic peptides [ie those which can be confused with self]. . . the chronic inflammatory environment may provide all factors necessary to induce and maintain autoimmunity. (Paroli et al 2000, p 202)

This effect of prolonged inflammation may provide the link between severe local reaction to immunisation and the development of longer-term systemic allergic and autoimmune reactions in prone individuals (see Section 7.2.1).

7.6.3 LINKS BETWEEN AUTOIMMUNE CONDITIONS AND IMMUNISATION

Although it is a rare complication, there are cases where the development of an autoimmune condition has been linked convincingly with immunisation as a triggering factor.

Older et al make several observations concerning this connection. The development of symptoms of connective tissue autoimmune disease (for example systemic lupus erythematosus) generally occur 1-3 weeks after secondary immunisations. This corresponds with the peak of the boosted immune response. Very few of these cases reported disease onset within the first three days after immunisation, which is when most neurological sequelae occur. This suggests that

“the mechanisms responsible for vaccine-related connective tissue disease may differ from those responsible for neurological sequelae” (Older et al 1999, p 136).

They also found no associations with age or gender. This was an unexpected finding, as autoimmune conditions in general are more common in women (Jacobson et al 1997). Both single agent and multiple or combination vaccines were implicated.

Some vaccines are reported to have a broad beneficial effect. Neonatal administration of BCG has been linked with a reduced incidence of type 1 diabetes; however vaccination after two months, and Hib vaccine have been implicated with increased risk (Singh 2000).

7.7 CONCLUSION

The association of immunisation with longer-term health consequences is a complex issue because of the length of time involved and the multiplicity of confounding factors. There is evidence that immunisation can trigger atopic and autoimmune conditions in prone individuals. It is generally possible to identify those with a genetic predisposition to atopy from family histories, but with autoimmune conditions this is more difficult and more research needs to be done on identifying factors. Fortunately, although it does occur, immunisation as a trigger of autoimmune conditions appears from current studies to be uncommon.

CHAPTER 8

MEASURING VACCINE EFFICACY: IMMUNOLOGICAL CORRELATES

8.1 INTRODUCTION

Before a vaccine becomes a candidate for commercial release for human use it must be proven to be 'safe' and 'efficacious'. In relation to vaccination "the term 'safety' has a variety of implicit meanings" (Rabinovich & Evans 1998, p 80) and is usually used without clarification. However, a relevant definition in legal use is the

> . . . relative freedom from harmful effect when a product is prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. (Rabinovich & Evans 1998, p 80)

This definition of 'safety' is not definitive, but open to interpretation depending on the circumstances. Various aspects of vaccine safety will be examined in this Chapter, and in Chapters 9 and 10.

A substance is considered efficacious if it is "producing, sure to produce, [the] desired effect" (Sykes 1976, p 330). The procedure that must be undertaken by the relevant companies to provide proof of vaccine safety and efficacy is rigorous,

extensive, and can currently be expected to take at least 10 years with no guarantee of ultimate acceptance (Sesardic & Mire-Sluis 2000). However, given that the desired effect is “generating immunological memory” (Ada 1994a, p 72), as discussed in Chapter 6, this undertaking that poorly understood at a technical level and lacks clear parameters for quantification.

A candidate vaccine must pass through six stages of testing before it can be considered for commercial release. These stages are common to most drugs and biological products for medical use. They are:

1. Research and Development – in the laboratory, studies in vitro and on animals (predominately mice).
2. Pre-clinical Trials – more extensive trials on “susceptible non-human hosts” (Ada 1994a, p 72).
3. Clinical Trials on humans.
    a) Phase I – on a limited number of volunteers to determine safety and immunogenicity.
    b) Phase II – more extensive studies in larger and sometimes more diverse groups.
    c) Phase III – efficacy studies in a population in an endemic area, or in specialized groups.

(from Ada 1994a; Gellin 1998)

After licensing, a vaccine is subject to post-registration surveillance, also known as Phase IV trials. The results of each of these stages are dependant upon the different factors that contribute to good scientific method, including:

Technical	Accurate measurement of the appropriate aspects of the immune response.
Methodological	Formulation of appropriate hypotheses. Selection of appropriate experimental or trial design.
Statistical	Appropriate analyses performed upon sufficiently large samples. Accurate analysis and reporting of any confounding variables.
Analytical	Unbiased reporting of results.

There are issues and problems associated with each of these factors in relation to the measurement and evaluation of vaccine efficacy. This chapter will focus on the technical issues relating to the measurement of immunological correlates of vaccine efficacy. Chapter 9 will focus on methodological, statistical and analytical issues raised by the various designs of vaccine efficacy trials.

There are two main technical problems with measuring immunological correlates of protection. The first is that immunologists are unclear about which indicators they should be measuring, and the second is that the results may vary not only between different measurement techniques, but also between different laboratories using the same techniques.

8.2 MEASURING VACCINE EFFICACY

According to Ada "to achieve high efficacy, a vaccine ideally should fulfill four immunological requirements" (1994a, p 76). These are, in simplified form:

1. Activation of antigen presenting cells.
2. A high yield of memory cells.
3. Generation of T-helper and cytotoxic T-lymphocytes to several components of the antigen to minimize the effects of individual differences in the MHC molecule (see Chapter 2).
4. Long term persistence of antigen, ensuring the steady production of antibody.

He notes that:

> Although successful live attenuated vaccines . . . probably fulfill all four requirements, many other vaccines do not. . . However, even a vaccine that only induces good memory responses could tip the balance in favour of survival by allowing a more rapid response after the challenge infection. (Ada 1994a, p 76)

All of this is fine in theory, but problems arise with attempts to quantify the ability of a vaccine to meet all, or any, of these requirements. An extensive examination of vaccine efficacy studies reveals that most are primarily epidemiological, and those that include a component of immunological analysis rarely provide an analysis as

detailed as the one suggested by Ada. They generally report on the level of immunoglobulin molecules (antibodies), specific for the pathogen targeted by the vaccine, that are present in the serum at a specified, but variable, time after immunisation. Further, they generally only report on the levels of immunoglobulin G (IgG).

The use of levels of serum antibody as an indicator of vaccine efficacy is based on the observed fact that antibody levels generally rise after both immunisation and natural infection. However, to assume that the degree of increase is directly related to the efficacy of the vaccine is to commit the logical fallacy *post hoc ergo propter hoc*. This is the fallacy of inferring that just because one thing occurred after another, the later was caused by the earlier (Barker 1974). Indeed, there is much evidence to show that the use of serum antibody as a measurement of vaccine efficacy may be misleading, and there are frequent references to this in the relevant literature. For example:

> The effect of the diminished antibody response on vaccine efficacy is difficult to assess because of the lack of known serological correlates of immunity. (Halperin, Eastwood & Langley 1995, p 95)

> Our data indicate the difficulty in evaluating observed efficacy on the basis of the presence or absence of high titres of specific antibodies . . . (Guiliano et al 1998, p 987)

> Correlation of long-term protection with high antibody levels is controversial, since protection against clinically significant HBV infection may persist even though antibody levels are low or undetectable. Furthermore, cell mediated immunity has been shown to be strongly involved in protection against viruses. (Brunel, Darbouret & Ronco 1998, p 2200)

The four most significant reasons for serum antibody being an inadequate correlate of protection will be discussed in detail below. They are as follows: Firstly, the immune response to any pathogen is very complex. Measuring serum antibody

levels only accounts for one aspect of the whole response, and there are increasing doubts as to its relevance as an adequate indicator of the whole.

Secondly, there are significant individual variations between individuals and between ethnic groups in serum antibody levels (Agbarakwe et al 1994). Such variations are considered normal.

Thirdly, the measurement of antibody levels specific to the particular antigen targeted by the vaccine fails to address the issue of pathogen variation. Wild pathogens are subject to mutation, and the killed or attenuated strains included in the vaccine may have limited relevance to new strains.

Fourthly, this specific measure fails to address the existence of an immunological resistance to infection that may be broader than the particular pathogen. For example, measles immunisation or survival from natural measles infection is known to have a general beneficial effect on the immune system, and to enhance survival from subsequent non-measles infections (Aaby 1995).

8.3 SERUM ANTIBODY AS AN INDICATOR OF PROTECTION

The fundamental problem with the use of specific serum antibody as an indicator of vaccine efficacy is that it only demonstrates a limited aspect of immune function. Also, this aspect of immune function has been shown to have an inconsistent relationship to protection from subsequent infection.

Antibodies are produced by B cells, and are involved in the maintenance of humoral immunity. Humoral immunity concerns defence against pathogens that operate outside the cells of the body, such as bacteria. Antibodies are not involved in the cell-mediated immunity that operates against pathogens like viruses that

invade cells (see Chapter 2). So serum antibody levels are inadequate as a measurement of the efficacy of vaccines that target viral pathogens such as polio and measles.

The serum concentration of antibodies may give some indication of the level of activation of B cells, and this may be related to the generation of memory B cells, but not necessarily so (see Chapter 6 for a detailed discussion on the problems of defining and evaluating immunological memory). Measuring antibodies leaves the whole area of T cell operation and cell-mediated immunity unaccounted for, along with the operation of antigen presenting cells, and antigen persistence. These were significant areas defined in Ada's (1994) requirements for the effective operation of a vaccine.

The measurement of serum antibody level has further limitations, in that it is primarily IgG that is measured, although several other types of immunoglobulin molecules, such as IgM, IgA and IgE, are also produced and play important roles at different stages of the immune response (see Sections 2.5, 7.4 and 7.5). There would seem to be a presumption behind this, that IgG is more important than other types of immunoglobulin because it is present in larger amounts. There is, however, "no firm correlation between these [IgG antibodies] and protection against clinical disease" (Heron 1994, p 389, see also Sections 2.92, 2.95 & 3.8).

Robbins, Schneerson & Szu make the counterclaim that "a critical level of serum IgG antibodies alone can prevent infectious diseases" (1995, p 1389), however they primarily base this assertion on the circular argument that

> . . . the only immune response required by FDA and other regulatory agencies for standardization of newly manufactured lots of vaccines is their ability to stimulate protective levels of serum antibodies. (p 1389)

They propose that the technical reason for this is

> . . . that licensed vaccines confer protective immunity by eliciting serum IgG antibodies that eliminate the inoculum by killing bacteria, “inactivating” viruses, or neutralizing toxins . . . on mucosal surfaces. (p 1387)

However, inconsistencies in results between similar trials (Clemens, Chuong & Feinstein 1983; Odelram et al 1993), and unexpected vaccine failures support the emphasis placed by Ada (1994a) on the involvement of other elements of the immune system such as other antibody classes and the involvement of cell-mediated as well as humoral immunity (Agbarakwe et al 1994; Donikian, McKee & Greene 1977; Sesardic & Mire-Sluis 2000). So does the fact that protection afforded by natural infection and live vaccines is greater than that induced by killed vaccines (Donikian, McKee & Greene 1977). All of this indicates that the standard physiological measurement of vaccine efficacy in terms of IgG concentration levels is inadequate.

8.3.1 PERTUSSIS VACCINE

This problem has been discussed with particular reference to pertussis vaccine because of the contradictory findings that:

> The two different whole-cell pertussis vaccines most commonly used in the U.S.A. have shown different immunogenicity profiles, but their use has been associated with control of pertussis without clear differences in respective efficacies. (Fritzell 1995, p 86)

whilst

> . . . vaccines that appear to have similar immunogenicity may show large differences in clinical efficacy. (Granoff 1999, p 87)

Researchers admit to uncertainty regarding which correlates to measure to determine vaccine efficacy and protection for the recipient:

> For pertussis protective immunity there is as yet no serological correlate. (Heron 1994, p 390)
>
> . . . the mechanism by which acellular pertussis vaccines confer protection is poorly understood. (Granoff 1999, p 87)
>
> Some manufacturers have attempted to equate the potency of acellular pertussis vaccines with antigenicity as measured by immunoassay for overall antibody production. There is as yet no objective evidence to equate such responses with clinical efficacy. Indeed such evidence as there is, suggests that there is no correlation. (Corbel 1994, p 357)
>
> The mechanisms of protective immunity against *Bordetella pertussis* infection following natural exposure or vaccination are still unclear. Immunogenicity studies during efficacy trials of pertussis vaccines in infants suggested that antibodies are not the sole determinants of resistance to this pathogen. Consequently, cell-mediated immunity (CMI) has been addressed . . . These studies suggest that CMI is probably an important host determinant of anti-pertussis resistance. (Ausiello et al 1998, p 466)

Although the need to evaluate cell-mediated as well as humoral immunity to pertussis is now well recognised, the issue has still not been formally addressed in vaccine evaluation regulations (Sesardic & Mire-Sluis 2000). The recognition of the involvement of cell-mediated immunity in resistance to pertussis is particularly interesting as pertussis is a bacterial infection. Current theory holds that only humoral immunity is involved in the defense against extracellular pathogens. The involvement of aspects of cell-mediated immunity indicates that immune responses to pathogens are more complex than previously believed.

8.3.2 Hib VACCINE

With Hib vaccine it is still the case that “the correlates of protection are not known” (Åhman et al 1999, p 2731), and:

> It is at present very difficult to estimate what the characteristics are of an immune response that is sufficient for protection after vaccination with Hib conjugate vaccines. (Käyhty 1994, p 400)

However, there is some evidence that anti-Hib antibody does correlate with "protection from invasive infections in humans" (Käyhty 1994, p 397). However, there is little agreement on suitable protective levels. Suggestions for protective levels range from 0.03μg/ml serum (below the limit that can be detected by the commonly used radioimmunoassay test) to 1μg/ml after vaccination, with considerable variations for individual and ethnic differences. The measurements here refer to anti-Hib polysaccharide antibodies (Käyhty 1994).

Polysaccharides are components of the cell surface, so the antibodies form in response to particular parts of the pathogen, not the pathogen as a whole. This is particularly important with young children, as their immune response to polysaccharides is limited (Vella & Ellis 1992). It is acknowledged that antibodies to Hib components other than polysaccharides can also contribute to protection (Käyhty 1994), although, as with pertussis, the immune response is more complex than current measurements and regulations are able to address.

> . . . it is likely that an elaborate interplay of many antibodies and cell types is necessary for an effectively balanced immune response capable of preventing invasive Hib infection. (Vella & Ellis 1992, p 15)

A considerable amount of research would be needed to clarify the situation, and this is considered unlikely to happen, because:

> Now that Hib conjugate vaccines have become available for infants . . . it is unlikely that additional efficacy studies will be initiated, [so] the protective level of anti-PRP [polyribosyl ribitol phosphate] following vaccination of infants with Hib conjugate vaccines will probably remain unknown. (Vella & Ellis 1992, p 19)

8.3.3 ANTIBODY LEVELS

There is a trend for studies to focus on being able to report that a vaccine stimulated high levels of antibody production (regardless of its functional activity).

> There is an unfortunate, but understandable, proclivity of immunologists to report the protective efficacy of their experimental vaccines at about ten days after the third booster shot, when it is maximal. However, . . . [as] exposure can occur from early age to any time in life thereafter, it is essential that vaccines prime a long term immunologic memory. (Bloom & Widdus 1998, p 483)

Although the stimulation of high levels of antibody production may give the impression that the vaccine is very effective, this is not necessarily the case (see Chapter 4 on Neonatal Tolerance). It has been shown that if a vaccine stimulates a high level of response there tends to be a more rapid decay of antibodies, which is not conducive to the development or maintenance of long-term immunity (Odelram et al 1994).

It has been reported that some vaccines demonstrate greater efficacy if exposure to wild pathogen occurs more than 70 days after immunisation than if exposure occurs within 17 days after immunisation, although circulating antibody levels are usually higher at 17 days than at 70 (Wassilak 1998). Different components of the immune system come in to play at different times after the initial infection or immunisation. For example, T-helper cell activity can be detected two to three days after infection and some memory T-cells can be detected after 14 days, whilst memory B-cells and antibody secreting cells reach a peak about three months after infection and can still be detected nearly two years later (Ada 1994b). This suggests that a more realistic evaluation of vaccine efficacy would be obtained from a range of immunological tests performed some months after immunisation, rather than from a simple reading of antibody levels obtained after a few weeks.

8.4 VARIATIONS IN INDIVIDAL AND POPULATION RESPONSE

There are considerable variations in immune responses between different ethnic groups, and between individuals within those ethnic groups (see Section 2.7). For example antibody responses to polysaccharide components of the Hib vaccine are poor in Native Americans, but excellent in Caucasians (Poirier, Poland & Jacobson 1996). Individuals with Asian heritage are likely to have poor responses to Hepatitis B vaccine (Hsu et al 1996).

Individual differences in response to immunisation are well documented, and most efficacy studies report a certain percentage of low or non-responders. In relation to Hepatitis B it has been shown that about 10% of recipients are non-responders (Hohler et al 1998), and in relation to Hib vaccines it has been found that:

> Hib conjugate vaccines are immunogenic in infants who are unresponsive to vaccination with the unconjugated type b polysaccharide capsule (PRP). . . This priming may occur in infants with low serum anti-PRP antibody responses to the conjugate vaccination and in infants whose antibody concentrations decline after conjugate vaccination. (Granoff et al 1993, p 663)

However, Åhman et al document a long-term increase in antibody response in a percentage of the study population:

> In children of 36 months of age only 13 to 36% of the antibodies measured one month after booster remained. . . Nevertheless, some children displayed over twofold increases in antibody concentrations from the two-year levels and, and, depending on the serotype, 5 to 18% of children had higher antibody concentrations at three years than at two years of age. (1999, p 2731)

A significant contributing factor to the observed variations is the wide genetic variation in MHC molecules with characteristic ethnic and geographic profiles (see Section 2.7; Hsu et al 1993; Worku et al 1997). Different MHC profiles are associated with both non- and hyper-responses to vaccines (Caillat-Zucman et al

1998; Hohler et al 1998; McDermott et al 1997; Mineta et al 1996). Research into the details and implications of these variations is very recent, and much still needs to be done.

The existence of such variations in response to any given vaccine means that even if immunologists were very clear about correlates of protection, there would still exist complications in determining suitable response levels and dose regimes for different populations. The situation, however, is even more complicated than this, because genetic variations are not the only reasons for the observed differences in responses to vaccine between different populations and individuals. Differences in diet, environment, social structure, public health policy and resources, and the epidemiology of disease within a population all contribute to characteristic response patterns (see Chapters 11 & 12). These factors have implications for the design of efficacy trials and will be addressed in detail in Chapter 9. The effects of variations in circulating wild pathogens will be discussed below.

8.5 PATHOGEN VARIATION

Circulating strains of wild pathogen vary over time and location. A standard vaccine formulation is not necessarily equally effective for all circulating strains. So, for example, when commenting on different efficacy results for Hib vaccine trials in Cuba and Brazil, one of the factors postulated was a variation in the bacteria.

> Brazil is a continent of a country, and we have polymorphisms of bacteria . . . There are some bacteria which we are unable to type. . . We are talking about cross-reactivity, but we have no good evidence to support the idea that we can protect based on cross-reactivity against the challenge given by a very broad range of polymorphic bacteria. (Prigenzi in Broome 1991, p 223)

This has also been discussed as a factor contributing to variations in the results obtained when evaluating pertussis vaccines.

> There is the question of whether the efficacy of some vaccines might be different for different strains of *B. pertussis* . . . we may presume that bacterial populations which differ in serotype will differ in various other ecological or biochemical characteristics – some of which might be relevant for vaccines. (Fine 1997, p 130)

This is another factor to consider, as epidemiological studies rarely report on the strains or subtypes of the target pathogen circulating in the local population at the time of a study, though this may have an impact on the observed results.

8.6 BROADER IMPLICATIONS OF VACCINE EFFICACY TRIALS

Vaccine efficacy trials usually have a very specific aim: to prove that a particular vaccine reduces the incidence of a particular disease in a target population, and sometimes to support this with evidence of increased levels of pathogen specific serum antibody in individuals who received the vaccine. This is understandable, as the primary aim is to provide proof of performance sufficient to satisfy licensing regulations. However, the result is that consideration is rarely given to any broader conditions surrounding administration of the vaccine, nor are potential non-specific effects of vaccine administration examined, unless they relate to claims of suspected adverse effects.

That vaccines may have non-specific, long-term effects on the general health of a population was highlighted by recent unexpected findings with the measles vaccine.

> Evaluations of immunisation programmes are usually based on the assumption that vaccines have an impact only against specific diseases. This assumption may not be correct for measles vaccine. (Aaby et al 1995, p 481)

It was found that recipients of a new high-titre measles vaccine, and particularly girls, had a reduced level of long-term survival compared with recipients of standard-titre vaccines. Recipients of standard-titre vaccines had an increased level of long-term survival, compared with unvaccinated children, in areas with high mortality. These effects were non-specific, that is, the variations in mortality levels were not associated with exposure to measles virus.

The explanation offered is that the measles vaccine provides a non-specific stimulus to the immune system which assists in providing protection from other infections (Aaby et al 1995). This is also an assertion that has been made about survival from natural measles infection (AVN 1998; Scheibner 1993). This proposition is compatible with the evidence presented above that the basis of immunity provided by a particular vaccine is broader and more complex than simply the production of pathogen specific serum antibodies.

There are other pathogen related issues that need more detailed consideration in the design and reporting of vaccine efficacy trials. These include:

- The background incidence of the disease.
- Currently circulating strains of the wild pathogen.
- The general epidemiology of the disease.
- Intensity of exposure (eg cases of disease in the household and local community)
- The proportion of the population that have already received a previously licensed version of the vaccine.
- That previous exposure to apparently unrelated pathogens may have an influence on response to the current vaccine.

The background incidence of the disease is an important consideration in determining the efficacy of a vaccine. The statistical analysis of the performance of

a new vaccine may be very different in a situation where there is a current outbreak, compared with a situation where the background incidence is very low. In a retrospective examination of several studies on 12 different pertussis vaccines accurate comparison of results was difficult because a number of parameters were not adequately reported. Background incidence of pertussis disease was one of them:

> The fact that pertussis appears in epidemic cycles makes it difficult to compare exposures in general population settings . . . (Fine 1997, p 130)

Related to this issue is the intensity and source of exposure to the pathogen.

> The influence of intensity of exposure on the performance of pertussis vaccines is unclear. One might expect that exposure intensity is much higher under conditions of household exposure than in a general population setting. (Fine 1997, p 130)

Aaby & Molbak (1992) found that more severe cases of measles in children were likely to occur if the contact was of the opposite sex, and that this overrode the effect of household exposure.

Currently circulating strains of the relevant pathogen is another important parameter that requires more thorough reporting. Studies rarely provide details of the particular strains of wild virus that are prevalent in the study population, although this could be important information in determining whether a vaccine is effective against some strains but not others (Fine 1997).

Related to this is the need to report on any other prevalent pathogens, as broader or cross-pathogenic effects may be discovered.

> It is likely that the Senegal children differed from the Europeans in terms of maternal antibody profiles and various intercurrent infections, which might

> have influenced their responses to pertussis vaccine antigens. (Fine 1997, p 130)

This is particularly important in areas where there is a high incidence of serious conditions such as Hepatitis B or malaria (NHMRC 2000a).

The general epidemiology of the target pathogen in the study population has also been shown to influence efficacy data. For example when a conjugate Hib vaccine was shown to have a protective efficacy of 87-90% in Finish infants, but only 34% in Alaskan infants it was thought that:

> Probably the most important reason for the low protective efficacy in the Alaskan study was the different epidemiology of the disease: it has a higher incidence and occurs at an earlier age in Alaska than in Finland. (Käyhty 1994, p 399)

It is also well documented that pertussis has a higher incidence where adults act as a reservoir (Cherry 1996).

8.7 LIMITATIONS OF ASSAYS

As noted in the discussion of Hib vaccine (Section 8.3.2) there exists a large range in estimates for protective levels of anti-Hib antibodies. The reasons for this include that they have been determined in different laboratories with slightly different test methods, and that there exist individual and ethnic differences (see Section 8.5). Also, in terms of the immunological tests used, there is a difference between the concentration of antibodies in serum, the degree to which these antibodies bind to the chemicals in the assays (their affinity) and their functional capacity *in vivo* (their avidity) (Käyhty 1994).

The standard method for measuring anti-Hib polysaccharide antibodies is the radioimmunoassay (RIA) and the standard serum used for this contains

> . . . a high concentration of fairly high affinity antibodies. In sera with lower affinity antibodies, a higher concentration may be needed to give equal binding of antigen – thus the real concentration is higher than the value given by the standard RIA. Low affinity antibodies are not uncommon in the sera of young infants: this may have accounted for differing results on the same sets of sera reported by different laboratories using slightly different assay methods. (Käyhty 1994, p 398)

As a result of these problems, other assay test methods, such as EIA (electroimmunoassay), are also used, and slight variations in procedure, chemicals, and methods of interpreting results all contribute to variations in the final results. This makes comparison of different study results a difficult process, even for those aware of the technical complexities involved (Edwards et al 1987).

There are therefore complexities in measuring serological efficacy for vaccines that target a single pathogen. The problems become even more evident with vaccines, such as acellular pertussis, which include multiple separate components of a pathogen, or multiple pathogens, as in DTPa.

> Some manufacturers have attempted to equate the potency of acellular pertussis vaccines with antigenicity as measured by immunoassay for overall antibody production. There is as yet no objective evidence to equate such responses with clinical efficacy. Indeed such evidence as there is, suggests that there is no correlation. (Corbel 1994, p 356)

The reason for this lack of correlation is probably that the assays measure antibody concentration, and affinity. This does not provide any indication of their functional activity (avidity) *in vivo* (Griffiths, Corbel & Xing 1999). It is recognised that only a certain proportion of IgG is functionally active, and that there is “no correlation between antibody avidity and concentration” (Agbarakwe et al 1994, p 209).

Assay tests for biological activity are used to evaluate the effect of a vaccine on the human immune system, and also to test for stability of vaccines in storage.

A vaccine needs to be stable under the specified storage requirements to maintain safety and maximum efficacy when used. Assays have limitations in assessing the stability of vaccines in storage, because they are unable to cover all aspects of product stability, for example detection of any degradation in the conjugation of the vaccine to the adjuvant.

> . . . due to their frequent lack of precision, they would often detect merely gross changes. Therefore, additional physico- and immunochemical analyses, particularly for the detection of degradation products that may cause adverse reactions . . . will be part of the requirements of the future guideline. (Haase 1994, p 374)

There has been a trend towards an increasing use of *in vitro* tests to reduce the use of animals, and to achieve greater accuracy. *In vitro* assays are being developed to replace the use of animals in the assessment of the strength of tetanus toxiods for use in vaccines. The development of this technology will be particularly useful for OPV, as currently almost 100 monkeys are sacrificed to test one batch. New methods include molecular testing and microchip technology to determine the strength (neurovirulence) of the batch and the proportion of virus that has reverted to the original virulent form. This technology can be applied to the testing of all live attenuated viral vaccines, but there are still problems to be overcome, as the ability to detect viral mutations is limited, and not yet sensitive enough (Proudnikov et al 2000).

There are a variety of different assay tests available, and they measure "seropositivity" or antibody levels in different ways. However, it is not just the means of measurement that may vary between trials, but the definition of seropositivity may also differ.

> Some studies accept a change from negative to positive, others require a two or four-fold rise in titre, others define a cut off in mIU. Thus the variety of tests used and differences in interpretation of results often make studies of immune response to vaccines difficult to compare. (Diaz-Ortega et al, 1994, p 37)

The World Health Organization's Expanded Program for Immunization encourages a standard measurement and the use of specified assay types, although this does not address the fundamental problem that "an antibody level which gives protection has not yet been established" (Diaz-Ortega et al 1994, p 37). Attempts to determine such protective antibody levels are complicated by the fact that the use of the same technique in different studies is no guarantee of easily comparable results.

Assays are so subject to variation that even the same test performed in different laboratories will produce results that show a statistically significant difference.

> Such assay variability means it is often difficult, if not impossible, to make sensible comparisons between clinical trials of . . . vaccines.
> (Diaz-Ortega et al 1994, p 36)

Gaines Das (1999), in an evaluation of quality control procedures, reports that two laboratories using reagents, distilled water, serum and microtitre plates from the same containers produced significantly different results. She cautions that:

> If the reference standard may differ by two-fold between two [apparently identical] assays this has important implications for the design of epidemiological studies. If antibody levels for serum samples from population A are measured in one assay, and those from population B are measured in a second assay, then it is possible to conclude, for example, that there is a two-fold difference between the two populations where none exists, or conversely to conclude that there is no difference between the two

> populations although there is in reality a two-fold difference . . . What is important is that the possible magnitude of the assay variability be recognized . . . (Gaines Das 1999, p 130)

Although setting “an international common working standard” (Sesardic & Mire-Sluis 2000, p 49) would eliminate an important source of assay variation, the degree of variability in assay tests is a problem that even the provision of standard serums and reagents cannot address. It is constantly cautioned throughout the literature that care should be taken when comparing results from different laboratories (Gaines Das 1999; Käyhty 1994; Klein 1999; Proudnikov 2000; Sesardic & Mire-Sluis 2000). This makes it very difficult to compare the results of vaccine efficacy studies done at different times, in different countries, and performed by different laboratories.

8.8 QUALITY OF VACCINES

The quality of vaccines has traditionally been assessed with various animal tests, including the monkey neurovirulence test for polio vaccine and the mouse weight gain test for pertussis vaccine. Significant efforts have been made to replace these with *in vitro* tests (Sesardic & Mire-Sluis 2000).

Some of the issues relating to vaccine quality in live viral vaccines include the possible introduction of contaminants from cell lines, and reversion to virulent strains. Contaminants from cell lines used for virus production include oncogenic or “deleterious DNA” (Sesardic & Mire-Sluis 2000) and prions that may lead to transmissible spongiform encephalopathy (McKenzie 1997).

Although every attempt is made to keep pure strains of attenuated virus in live viral vaccines, there is always the possibility for reversion to the original virulence. This

is more prevalent in strains that have undergone fewer mutations to reach the attenuated state. For example the attenuated poliovirus type 3 in OPV is the strain most frequently associated with cases of vaccine associated paralytic poliomyelitis because it is genetically more unstable than the other two. It differs from the wild virus by 10 mutations and only 2 mutations may be necessary for neurovirulence. Type 1 virus, however, differs by 56 mutations and up to 6 mutations are needed to revert to neurovirulence (Faden 1993). It is noted that:

> Any batch of oral poliovirus vaccine contains some small but measurable amount of neurovirulent revertants. If the revertant content exceeds a critical threshold, neurovirulence of the vaccine batch increases to an unacceptable level. (Proudnikov et al 2000, p 64)

For poliovirus vaccine this critical threshold is less than 10% (Proudnikov et al 2000).

Vaccine purity is easier to characterise with vaccines manufactured from pathogen components, such as acellular pertussis, or Hib conjugate vaccine. This is because the components are carefully characterised.

> Acellular pertussis vaccines, for example, consist of highly purified and highly characterized antigens. Tests are in place to ensure that each lot of vaccine antigen has properties consistent with lots shown to be protective in clinical trials. Toxicity is determined, where applicable, using highly sensitive and specific tests. This is in contrast to whole-cell vaccines, for which the fairly unspecific mouse weight gain test is used. (Dellepiane, Griffiths & Milstein 2000, p 156)

Assurances of vaccine purity become more complex with combined vaccines as there are many more components. It is also possible that the effects of single components combine in a synergistic effect thus increasing the risk, and/or the severity of adverse events. The primary means used to detect problems with combined vaccines is through large post-licensing population studies and the use of adverse event reporting systems, and it is acknowledged that for vaccines currently in use, “very little information is unbiased” (Salmaso, 1994, p 407). The

inadequacies of these methods will be discussed in Chapters 9 and 10. Identifying the specific component or components responsible for an adverse event "can be extremely difficult" (Salmaso 1994, p 407). As the trend in vaccine development is clearly towards the production of combination vaccines in preference to single vaccines, Salmaso calls for debate on the relative safety of combination compared to single vaccines. He also calls for debate on whether

> . . . the criteria for evaluating the safety of combined vaccines [should] be universal, or should they differ according to the socio-demographic characteristics of the country in which the vaccine will be used? (Salmaso 1994, p 408)

The recent debate in the United Kingdom over the relative benefits of the use of single vaccines for measles, mumps and rubella versus the combined MMR vaccine is an indication that resolution of this issue has not progressed far on a national level, let alone an international one. Representative of those in favour of the use of the combined vaccine in the United Kingdom are Elliman & Bedford 2001 and Kmietowicz 2001, and amongst those voicing concerns about its safety are Fletcher 2000 and Wakefield & Montgomery 2000.

8.9 CONCLUSION

The scientific and medical establishments make genuine efforts to ensure that the paediatric vaccines they produce and administer are 'safe' and 'efficacious'. The problem lies in determining what constitutes 'safe' and 'efficacious', and how to measure these parameters.

Current empirical methods of measurement are inadequate, as antibody counts do not correlate strongly with protection from the disease and the results of assay tests vary significantly between different laboratories. The comparability of efficacy studies is limited by inadequate reporting of

possible confounding factors such as background incidence of disease and currently circulating strains of pathogen. The current trend towards the development of combination vaccines in preference to single vaccines adds further complexities to the issue.

CHAPTER 9

EPIDEMIOLOGICAL STUDIES OF VACCINE EFFICACY

9.1 INTRODUCTION

Epidemiological studies of vaccine efficacy endeavour to quantify vaccine effectiveness by examining the effect of the administration of a particular vaccine (or vaccine combination) on the incidence of the target disease(s) in the study population. Some epidemiological studies incorporate an examination of the serum antibody levels in a selection of the study population (thus raising the issues associated with serum antibody measurement as outlined in Chapter 8), but most do not. Vaccine efficacy is measured in terms of reduction either in the incidence or severity of reported cases of the disease under study (Fine 1997; Chang, Guess & Heyse 1994; Halloran et al 1991; Miller 1999).

Epidemiological studies of vaccine efficacy are affected by all the difficulties usually associated with large population studies, including accessing and tracking subjects (see Section 9.3.4). They also possess their own characteristic set of issues

including the accurate definition of relevant cases of disease and evaluation of case severity (see Sections 9.3.2).

9.2 TRIAL DESIGNS

There are a variety of styles of epidemiological studies that can be conducted, each with its own benefits and problems. The three most common types of study are:

- Randomised double-blind control trials.
- Cohort studies.
- Case-control studies.

9.2.1 RANDOMISED DOUBLE-BLIND CONTROL TRIALS

In terms of providing maximum scientific validity, the ideal method is the randomised double-blind placebo control trial. In this type of trial subjects are randomized to receive either the vaccine or a placebo, and both subjects and participating health professionals are unaware (blind) as to which has been administered. Those who do not receive the vaccine receive a true placebo, eg saline, that is usually made to look similar to the vaccine. Although this is the ideal design, its use is mainly restricted to testing vaccines for diseases for which there is no prior licensed vaccine (Smith, Rodriques & Fine 1984). However, even if the vaccine and placebo appear similar, sometimes the low rate of reaction to the placebo can have the result of unblinding the trial (Fine 1997). To avoid this, the subjects who do not receive the vaccine may be administered a “placebo” that consists of the same adjuvant base as the vaccine, but which lacks the antigenic component (Midthun, Horne & Goldenthal 1998). Using the same adjuvant base provides similar results to a true placebo in terms of evaluating the effectiveness of the antigenic component of the vaccine, and can have the added benefit of highlighting the proportion of reactions that can be attributed to the adjuvant rather than the antigen.

Sometimes there are practical reasons why it is not possible to test with a placebo. For example the BCG vaccine used for tuberculosis leaves a scar or pigmented area on the skin at the injection site, and a comparable placebo cannot ethically be administered (Clemens et al 1983). It is therefore impossible to do a true double-blinded study for BCG.

In cases where there already exists a licensed vaccine for the target disease the use of a placebo in trials is less common. This is because, increasingly, it is not considered ethical to withhold from subjects a preventative measure with proven efficacy (Fine 1997; Karvonen, Cepaitis & Tuomilehto 1999). In these cases the control subjects may receive a different vaccine for the same disease (Midthun, Horne & Goldenthal 1998) or more than one experimental vaccine may be simultaneously trialled. This is why, for example, the new acellular pertussis vaccines, or new combination vaccines are generally trialled against the currently licensed vaccines (Aoyama 1996; Fine 1997; Granoff et al 1993; Jadhav & Gairola 1999; Miller 1999).

This is also the predominate situation with Hib vaccines. There are several Hib conjugate vaccines, but only one was tested with a double-blinded randomised trial against an unvaccinated control group. This was the PRP-OMPC vaccine tested in North American Indians (see Santosham et al 1987). Another trial, conducted in Finland was unblinded, with participants randomised according to birth-date. There were no unvaccinated controls as half received the PRP-D vaccine and half received HbOC vaccine. The other trials have been described as “open studies” (Black et al 1991). Efficacy rates were determined by relative disease incidence in the different groups. Efficacy studies for Hib conjugate vaccines from nine separate studies have reported efficacy rates from 35%-100%. Anti-hib antibody levels varied from 0.18 - 22.4 μg/ml after three doses (Vella & Ellis 1992). Estimates of

protective antibody levels vary from 0.15 -1.0 μg/ml. Given that they are testing different conjugate vaccines and that the study designs are so different and that the antibody levels were determined using different tests in different laboratories, the results are difficult to meaningfully compare.

Although randomised, double-blind control trials are considered the most scientifically valid means of evaluating vaccine efficacy, they have limitations when used in any population study, as well as some limitations that are particular to their application in measuring vaccine efficacy. These include:

<u>General limitations of randomised control trials when used in population studies:</u>

- They are very costly to run. (Smith, Rodrigues & Fine 1984)
- The health-care professionals who participate may be unrepresentative, as may be the study participants.
- Participants may receive better than usual care, regardless of the formulation they are randomised to receive, simply because they are in the trial.
- The trial may be influenced by unrecognised confounding factors.

Limitations of randomised control trials that are particular to studies of vaccine efficacy:

- They are rarely large enough to measure infrequent adverse reactions. For example the recent withdrawal of the rotavirus vaccine after it was found to increase the risk of intussusception. (Kramarz et al 2001)
- They are generally of short duration (weeks or months) and so therefore are unable to detect longer-term consequences of immunisation.
- The conditions under which the vaccine is administered are usually optimal in terms of vaccine quality, transport, storage and administration, and therefore may differ in many ways from the conditions experienced in everyday health care. (Smith, Rodrigues & Fine 1984)

(from Black 1996, unless otherwise stated)

Some of these issues are addressed by the use of other epidemiological study methods, such as cohort and case-control studies. These types of studies have been criticised on the grounds that they do not have the scientific rigor of the randomised control trial:

> For some, the double-blind randomized trial is the only way to test a causal relationship with human subjects, and there is a tendency to disparage

> other designs. This is an unrealistic stance. Most of our understanding of human health in terms of treatment, cause and health care delivery comes from observational studies. (Moon & Gould 2000, p 70)

> The widely held view that experimental methods (randomised controlled trials) are the "gold standard" for evaluation has led to the denigration of non-experimental methods, to the extent that research funding bodies and journal editors automatically reject them. I suggest that such attitudes limit our potential to evaluate health care and hence to improve the scientific basis of how to treat individuals and how to organise services. (Black 1996, p 1215)

Cohort and case-control studies offer advantages in terms of cost, access to larger sample sizes and the potential for longer-term follow-up on the study population, and therefore have the capacity to provide useful information. The double-blind control trial may not be the most effective means of assessing the effectiveness of vaccines, as the information they provide is limited. There are a wide range of factors that influence the efficacy of a vaccine, and even the current designs of cohort and case-control studies have considerable scope for improvement in terms of usefulness and comparability of data collected. These issues will be addressed in more detail in Section 9.3. The effects, and inadequacies, of reliance on current scientific experimental practice will be discussed in Chapter 14.

9.2.2 COHORT STUDIES

Cohort studies track exposed (vaccinated) and non-exposed (unvaccinated) subjects over time and monitor the development of adverse reactions or disease. These are the most common types of population studies undertaken to evaluate vaccine efficacy (Moon & Gould 2000).

The follow-up time can vary from a few weeks or months (Henderson et al 1999) to over ten years (Karvonen, Cepaitis & Tuomilehto 1999), and the population sample sizes may be very large, for example tens of thousands of people (Black et al 1991;

Vella & Ellis 1992). These studies may be prospective or retrospective. A prospective design is one that follows subjects from the time of vaccination, whereas a retrospective design uses historical data to track down individuals who either did or did not receive a certain vaccination in the past and evaluate their current health, and perhaps follow-up future outcomes. This is the sort of study that has been done to evaluate whether exposure to SV40 (simian virus 40) from oral polio vaccines administered prior to 1962 has resulted in increased rates of cancer in recipients. There does appear to be some connection between exposure to SV40 and mesothelioma, although the exact nature and extent of this relationship is still being debated (see for example: Carbone, Rizzo & Pass 1997; Olin & Giesecke 1998; Pepper et al 1996; Strickler et al 1998).

9.2.3 CASE-CONTROL STUDIES

Case control studies differ in that they start with a sample that has a certain disease or health condition, and a sample that is healthy or unafflicted to act as a control. The two groups are then examined for differences in terms of past exposure to risk factors (Moon & Gould 2000). This study design is sometimes used to evaluate a suspected long-term adverse effect of a vaccine. For example the recent study by Kaye, Melero-Montes & Jick (2001) which evaluated the potential connection between MMR vaccine and autism as has been proposed by Wakefield et al (1998), and found no evidence of a connection between the two conditions.

9.3 ISSUES RELATING TO STUDY DESIGN

9.3.1 VACCINE ADMINISTRATION

The way a vaccine is administered has been shown to have a significant impact on the performance of the vaccine, and yet the details of administration are rarely

reported on in published studies (Poirier, Poland & Jacobson 1996). These details include:

- Dose.
- Route of administration.
- Injection site and technique.
- Needle gauge and length.
- Storage.
- Handling and cold-chain details.
- Concomitant administration of other vaccines, drugs or biological products. (summarised from Poirier, Poland & Jacobson 1996)

For example with Hepatitis B vaccine, injection in the deltoid muscle has been shown to be significantly more effective than injection in the buttocks, whereas for DTP vaccines injection in the thigh results in fewer local reactions. There is also evidence that injection of a vaccine deep into a large muscle is more effective than a shallow injection under the skin, and for this reason the length of needle used has been shown to have an influence. The use of a longer needle, for example, means the vaccine is more likely to be released into muscle tissue, thus avoiding some adverse reactions:

> Pediatric subjects vaccinated with DTP-polio in the thigh have significantly more local reactions using a .58" long needle compared to a 1" needle, and have an increased rate of sterile abscess formation. Local reactions are twice as frequent after deltoid versus thigh injections in children after receiving DTP-containing vaccines.
>
> (Poirier, Poland & Jacobson 1996, p 26)

Details about storage and handling are also important, as many vaccines are very temperature sensitive, particularly the live viral vaccines such as MMR and IPV (Health Canada 1995; NHMRC 1997). Lot numbers of vaccine batches also need to be provided because there can be significant variations in potency between different lots of the same vaccine from the same company.

> Recently 16 lots of *H. influenzae* type B [Hib] vaccine, representing 23% of the lots distributed over a 2 year time period, were reported to have diminished immunogenicity. These important findings were discovered after the vaccine had been used in the population clinically and in large clinical research trials where the lot number was recorded and could be correlated with immunogenicity. (Poirier, Poland & Jacobson 1996, p 27)

Records also need to be kept on simultaneously administered vaccines, and any other drugs or biological products that participants may have received, as these may influence the efficacy of the vaccine. For example a single dose of gamma-globulin may inhibit the antibody response to measles vaccine for at least six months (Poirier, Poland & Jacobson 1996), and simultaneous administration of DTP and Hib conjugate has been shown to result in a 60% reduction in "the geometric mean of PRP [polyribosyl ribitol phosphate, a Hib polysaccharide] antibody titers" to the Hib component. On average, the resultant level was still considered to be protective, although it was thought that "an antibody decline below protective level might occur slightly earlier" (Fritzell 1995, p 85).

Study design details of this nature may seem trivial and therefore not worthy of inclusion, but they can make a significant difference to the outcome, and therefore need to be included to enable accurate comparisons between studies in different populations.

9.3.2 CASE DEFINITION

An important part of any trial design is the use of a case definition for evaluating the occurrence and severity of cases of the target disease. For some diseases, such as measles, cases are fairly obvious and easily identified and confirmed. Other diseases, such as pertussis, are less easy to clinically identify and therefore present a variety of problems. In the same way that it is not a standard practice to report on the details of vaccine administration (see Section 9.3.1), it is also not a standard practice to outline the case definition used. This contributes to the

problems that occur when trying to compare studies conducted in different populations.

The most common case definitions used are those provided by WHO. These are carefully compiled to cover, in most cases, clinical, microbiological and epidemiological factors. These case definitions, along with standardised preparations and guidelines for the interpretation of assay tests, form the general basis for world-wide standardisation of results.

> The World Health Organization establishes nonbinding international norms for vaccine acceptability that are adopted by many countries. (Petricciani et al 1989: S524)

However, because there are no international regulations governing their use in studies, they are generally, but not necessarily, used. It is therefore important for studies to clearly state the case definition they are using to enable comparisons to be made.

Even a common use of WHO case definitions does not make for a clear situation. Different aspects of the definition may be used with varying effect. For example in a comparison of seven studies on pertussis, all of which used a variant of the WHO definition, Salmaso et al found that:

> The epidemiological criterion of confirmation has been shown to be of little use, beyond the evaluation of vaccine efficacy in household settings, in that it adds little to the definition's sensitivity. In the Stockholm I Trial, use of the epidemiological criterion resulted in the inclusion of only 10 out of 737 pertussis cases. (1997, p 136).

However, in large population studies it is not feasible to have laboratory (or microbiological) confirmation for all cases, so in these situations there is usually reliance on the clinical aspect of the definition. Although the clinical case definition used in a clinical trial

> . . . must be highly specific, it may not be sufficiently sensitive or practical for surveillance activities. Even given the inherent limitations of routine surveillance, the type of case shown to be prevented during a clinical trial may not correspond directly to the decrease of incidence observed in the routine surveillance system when the same vaccination is provided. (Salmaso et al 1997, p 135)

The reason for this is that although the case definition may be specific, medications administered for treatment of symptoms may alter the clinical course of the disease. Also, once the population is vaccinated there is often a modification of the clinical course of the disease, sometimes to the point where it is not easily recognised, thus affecting surveillance results and estimations of efficacy.

Whooping cough, for example, is defined in terms of:

> . . . median number of days with a specific symptom (cough, paroxysmal cough, apnea, whoops, etc.) and by total duration of cough (of any type) for each episode. (Salmaso et al 1997, p 136)

However, the characteristics of the disease varied from this in vaccinated children, and furthermore they showed variations between vaccines, particularly acellular pertussis vaccines that are comprised of different antigenic components. As long as these cases are still recognised, then

> . . . the proportion of confirmed infections not meeting the clinical criterion for cases of pertussis can provide some major indications on which type of protection is induced by the vaccines . . . and on which type of case will be prevented by the vaccines. (Salmaso et al 1997, pp 139-40)

The problem here is how to build into a study a process that formally recognizes cases of the disease that do not fit the specific case definition being used by the study! This highlights the significant issue that estimations of vaccine efficacy

determined by population studies are highly dependent upon the case definition used.

Results of population based efficacy studies should be treated with care because a low observed vaccine efficacy may be either the result of a very sensitive active surveillance system that picks up even mild cases of the disease, or it could be because the vaccine is indeed not very efficacious. Conversely a high observed vaccine efficacy may be a result of a specific and rigidly applied case definition that does not detect moderate or mild cases, or it may truly be highly efficacious. Infection with a pathogen is a parameter that can be objectively assessed, but inclusion on the grounds of severity of symptoms involves subjective judgements and can have a significant effect on the outcome of a vaccine efficacy trial. It has also been noted that:

> [The] case definition of pertussis . . . developed by the World Health Organisation for use in vaccine efficacy trials . . . eliminates some laboratory-confirmed cases from efficacy calculations. Because these cases are more common in vaccinees than in controls, vaccine efficacy appears better than it truly is whereas less effective vaccines seem comparable with their more effective counterparts. (Cherry 1997, p S90)

For this reason:

> Even with a “common” case definition, comparisons between efficacy studies can be limited. . . We have been led to the pragmatic conclusion that whatever case definition is chosen in theory, in practice the cases detected and counted are filtered by the study design and its applied conduct in the field, which could provide the opportunity for selection bias. (Salmaso et al 1997, p 141)

In one respect the use of narrow case definitions is acceptable, because it is the severe, life-threatening cases of the disease that the vaccine is aimed at eradicating. With sound information, most people would realistically accept a

vaccine as being efficacious if it reduced the severity of a disease without necessarily eradicating it.

> It should be noted that mothers in many instances have had a better perception of the epidemiological reality . . . mothers have clearly experienced that vaccinated children have 'mild' measles, thus suggesting that partial immunity is possible . . . (Aaby 1995, p 684)

9.3.3 REPORTING ADVERSE EVENTS

In most vaccine efficacy trials, adverse events are only counted after the completion of the final dose of vaccine. There are often three or more doses in a course, spread over a period of several weeks or months. This means that any reactions to the earlier doses may be missed from the data, especially if participants drop out as a result. In the field trial of OPV conducted in the 1950's, 10% of adverse events were excluded from the data because of this design feature (Peduzzi, Donta & Iwane 1997).

In a review of 35 vaccine efficacy trials, Peduzzi, Donta & Iwane found that:

> Most of the studies reported the results of an efficacy analysis that counted cases of illness postvaccination only in fully vaccinated subjects and rarely gave a complete accounting of all cases that occurred in all vaccinees. (1997, p 398)

However, it is important that studies provide a complete account of all adverse events to enable full analysis of issues such as increasing severity of adverse reactions with subsequent doses (as is documented with DTP, see NHMRC 1997; AVN 1998). Also, with some diseases there has been "potentiation of disease by vaccination" (Peduzzi, Donta & Iwane 1997, p 412) that is exacerbation of cases of the target disease in vaccinated individuals. This has been a significant concern in the development of a vaccine for respiratory syncytial virus (RSV) (Openshaw & Hussell 1998).

Another concern is the limit of the range of adverse effects that are examined by efficacy trials. The aspect of trial design that investigates the occurrence and frequency of adverse effects tends to be influenced by the expectations of the researchers. Trials are generally designed to demonstrate "that expected adverse effects with short latency do not occur unacceptably often" (Clemens et al 1996, p 391). The adverse effects examined are usually ones that:

> . . . are expected on the basis of earlier studies, that occur shortly after vaccination and are frequent, and that are easily measured with symptom questionnaires and other available instruments. (Clemens et al 1996, p 391)

This means that even a fairly frequent adverse effect may remain undetected if it is not expected. Effects that are unexpected, rare, or take some time (weeks or months or years) to develop are unlikely to be detected in the Phase III pre-licensing trials unless their effect is dramatic, as for instance the potentiation of disease seen in the recipients of vaccines for RSV.

> The populations enrolled in clinical trials typically are small and homogenous, and their members are rarely followed for long periods, precluding detection of events that are uncommon (less than 1 per 1, 000 to 10, 000 vaccine doses) or have delayed onsets. (Wassilak et al 1995, p 377)

Rare or unexpected effects may be detected in a Phase IV post-licensing study, but these are infrequently done as they are costly, and from the manufacturing company's point of view there is little motivation to perform further studies after licensing is obtained (Wassilak et al 1995). Post-licensing studies tend to be performed in response to the perception of a problem. This perception may arise from the public, and/or from health practitioners who notice a temporal, and therefore potentially causal link between immunisation and a particular health issue. This has happened with issues such as Hib vaccine being examined in

relation to an increase in the incidence of type I diabetes (see Classen & Classen 1999; Gardner et al 1997; Karvonen, Ceptaitis & Tuomilehto 1999; Tuomilehto et al 1995) and MMR vaccine being putatively linked with autism and inflammatory bowel disease (see Chen & DeStephano 1998; Fombonne 1998; Lee et al 1998; Wakefield et al 1998). These debates often remain to some extent unresolved, while focussing on the details of study design, statistical analysis and the ethics of raising public concern over potential (or actual) vaccine adverse effects.

One way to obtain post-licensure surveillance without the expense of specific epidemiological studies is provided by the development of large health data-bases. These are compiled from subscriptions to health care plans and preventative procedure registers. They make large cohort studies economically feasible, and allow for study designs to be varied and reevaluated with ease. They have a wide range of applications including detection of adverse drug interactions, and long-term outcomes of various surgical procedures (Wassilak et al 1995). They allow for the examination of rare and unexpected adverse effects of a licensed vaccine, and also for the assessment of adverse effects of combined or simultaneously administered vaccines. This is particularly valuable because:

> For combined vaccines, identifying the specific component or components responsible for the adverse event can be extremely difficult. (Salmaso 1994, p 407)

Currently investigation is being carried out on more than 35 conditions that have been potentially linked with the administration of licensed vaccines (Wassilak et al 1995).

9.3.4 SELECTION OF STUDY POPULATION

An important consideration in the design of any style of study is the choice of population in which it is conducted. The important factors here are race and ethnicity, age, sex, socioeconomic status and health (Lin & Kelsey 2000). The most important issue is, once again, accurate reporting of population characteristics in the study to enable useful comparisons to be made between studies, and also to enable any factors that are related to these variables to be clearly identified.

9.4.3.1 Race and Ethnicity

The race(s) or ethnic group(s) of participants enrolled in a study is an important variable to define, but accurate assessment of it is subject to difficulties. The definition of groups depends heavily on the categories provided on census and other official forms. For example, in the United States “Asian” may cover racial and ethnic groups as diverse as Chinese, Japanese, Vietnamese, subcontinent Indians etc. Similarly “Hispanic” is a very generalised term and may cover individuals from almost any of the countries of the South American continent, and “White” covers a similarly broad range of backgrounds. Individuals may be a blend of two or more groups and identify to varying degrees with one or other of them, similarly individuals may be born in one country and reside in another and identify with either or both and may be citizens of a third. This means there will be considerable variation within respondents to the same category on a questionnaire or census form.

It is important to gain some indication of the mix of race or ethnic groups enrolled in a vaccine efficacy trial because there are well-documented differences in characteristic immune responses between different races and ethnic groups. These

differences may occur even between ethnic groups that live closely together, and may be very disease specific (Hsu et al 1996).

For example aboriginal Taiwanese and nonaboriginal Han Chinese in adjacent villages showed different responses to HBV, with children of mixed parental origins showing levels in between (Hsu et al 1996). There was no corresponding variation for Japanese encephalitis or diphtheria vaccines.

Similar findings have been made for Hib vaccine in America:

> Antibody response to polysaccharide Haemophilus influenzae type b vaccine is poorer in Native Americans, but excellent in Caucasians. Failure to obtain and report ethnicity/race information would have prevented the discovery of this important finding. (Poirier et al 1996, p 27)

> The antibody response of Chilean infants to a single dose of Haemophilus influenzae type b capsular polysaccharide-tetanus toxoid conjugate vaccine is substantially higher than that observed among infants of similar age from the USA. (Levine et al 1997, p 325)

Chileans therefore vary substantially from Native Americans with presumably "white" infants from the USA in between. Many Chileans would also be Amerindians, thus increasing the complexity of the situation. The variation is linked with the use of tetanus toxoid as a carrier, the use of diphtheria toxoid as a carrier did not provide the same response. In Chilean infants "low maternal education and a greater number of persons in the home are significantly associated with the superior responder phenotype" (Levine 1997, p 325), so the variation appears to be a mix of both physiological and environmental factors.

In a study of the variation in T cells between populations in Bangladesh, Ethiopia and Sweden, Worku et al concluded that:

> The data suggest that environmental or genetic factors are important bias factors to be considered in immunphenotyping studies. Possibly differences in the pattern or level of microbial challenge, as well as nutritional factors, may lead to different adaptive changes in the immune response. The potential influence of such immune adaptation on the response to vaccination or pharmaceutical therapy may be important in the development of new strategies of medical intervention in different geographical regions or ethnic groups. (Worku et al 1997, p 618)

The issue of racial variations in characteristic vaccination response has been recognised, and there have been some studies done which document notable variations that have come to the attention of researchers (eg Hsu et al 1996; Stephens et al 1995; Thuc et al 1994; Worku et al 1997), however there is considerable scope for investigating why these differences occur, and to explore the possible implications for vaccination dose or scheduling.

Those responsible for study design need to be sensitive to the cultural characteristics of the study population as items on a questionnaire may be differently interpreted, for example terms such as “fever” or “irritability” may be open to different interpretations by different ethnic groups.

9.4.3.2 Age

The age at which a vaccine is administered is an important consideration, and may have a significant effect on the performance of the vaccine. This is because the immune system undergoes constant developmental changes (see Chapter 5) and maternal antibodies are present in the infant’s serum for some months after birth (Roitt 1991, Ch 11).

Age at administration is a parameter that has a good report rate in efficacy trials. Poirier et al (1996) found that 94% of trials reported the age of study participants.

Some studies are conducted specifically to determine the most effective administration schedule (Aaby 1995; Gellin 1998), but decisions determining the age of participants can be influenced by many factors. These include accessibility of study population, methods of randomisation (sometimes certain birth cohorts are used) and existence of licensed vaccines for the target disease.

A primary consideration with Phase III trials is to make sure the vaccine is trialled under optimal circumstances. In particular

> . . . care is taken to isolate administration of the tested vaccine from any vaccines, drugs, or dietary practices anticipated to interfere with vaccine-induced immune responses. (Clemens et al 1996, p 391)

To achieve this, new vaccines are often trialled outside of the standard vaccine schedule.

Trial situations are therefore often very different to the practicalities that are faced once a vaccine is licensed. It is widely recognised, and a matter of increasing concern, that the current childhood immunisation schedule is already crowded, so when the vaccine is licensed, there is a great deal of pressure to incorporate it into the existing childhood vaccination schedule. Further to this, there is increasing pressure to incorporate a new vaccine into a combination formula to reduce the number of injections and ensure optimal acceptance (Daum, Jain & Goldstein).

> The potential benefit of fewer injections, a decrease in the number of physician/clinic interactions necessary to comply with recommended immunization schedules, decreased administration costs, and simplification of medical record maintenance are some obvious reasons for the interest in developing combination vaccines. (Daum, Jain & Goldstein 1995, p 383)

> . . . the increasing number of vaccines proposed for inclusion in the infant immunization schedules has made the development of combination vaccines mandatory. (Corbel 1994, p 353)

For these reasons, studies on the optimal age for vaccination administration cannot always be feasibly implemented. For example studies have shown that administration of pertussis vaccine “the 3-, 5- and 12-month schedule was more effective in providing protection than the 2-, 4- and 6-month schedule. This finding was expected since the third dose at 12 months is considered a booster dose, comparable to the fourth dose provided in the United States at 15 to 18 months” (Gellin 1998, p 50). In Great Britain they follow a 3, 5 and 12 month schedule for pertussis, while in Australia, as in the United States, pertussis is administered at 2, 4 and 6 months with a booster dose at 18 months (NHMRC 2000a). Any changes to an existing schedule are regarded as extremely difficult to make because of the potential for confusion. This issue will be discussed in greater detail in Chapter 10.

9.3.5 BACKGROUND INCIDENCE OF DISEASE

An evaluation of the background incidence of disease “sets the foundation for efficient design of a clinical trial” (Wassilak 1998, p 80). It is important to establish accurate figures for incidence and severity of disease in the unvaccinated population, because it is the observed differences in these parameters after the administration of the vaccine that are used to provide measurements of vaccine efficacy.

Another important parameter is the current circulating strains of the target pathogen. There are many circulating wild strains of, for example measles or polio, with new ones evolving and mutating over time. The attenuated strains used in the vaccines remain fairly consistent and may be more effective in providing protection against some wild strains than against others.

This may be a confounding factor where there are wide ranges in estimates of vaccine efficacy, however it is rarely reported, and was not listed as a trial parameter in the study evaluation by Poirier et al (1996). Clemens et al (1983) listed it as a potential factor in the wide range of protective efficacy values reported for BCG vaccine, although they decided that general quality of study design was a more significant factor. Similarly with trials for a vaccine against meningococcal disease:

> We can speculate about the diversity in results . . . one [factor] is the heterogeneity of the strains. May be this is one point which has been neglected in the discussion. (Prigenzi in Broome 1991, p 223)

Another consideration related to the background incidence of the disease is the general immunity of the unvaccinated population. If a pathogen circulates widely there is likely to be a relatively high level of natural resistance to it. If it is rare in the community then resistance will be low. This is one of the fundamental assumptions upon which immunisation is based. Immunisation is designed to artificially provide a widespread mild exposure to the pathogen to increase the immunity of the general population, this is generally known as ‘herd immunity’. The general exposure level of the population needs to be determined before the trial, as naturally acquired immunity can confound study results. This is a factor that was seen to play a role in the observed differences between the protective efficacy in Finish (87-90%) and Alaskan (34%) infants (see Section 8.6) In this example, when a conjugate Hib vaccine was shown to have a protective efficacy of 87-90% in Finish infants, but only 34% in Alaskan infants it was thought that:

> Probably the most important reason for the low protective efficacy in the Alaskan study was the different epidemiology of the disease: it has a higher incidence and occurs at an earlier age in Alaska than in Finland. (Käyhty 1994, p 399)

Generally, as in these cases, variations in circulating wild strains are considered as explanations of anomalous results after the fact, and it is usually impossible to check back to what the circulating strains were. A far more effective approach would be to note and report on the situation at the time. This would provide useful information about the effectiveness of a vaccine against particular strains of the disease. This is particularly relevant to vaccines such as the Hib conjugates and acellular pertussis where there are many versions and these may vary in their effectiveness against some strains of the disease (Granoff et al 1992; Vella & Ellis 1992).

9.4 INTERPRETATION OF RESULTS

The principal problems with both serological and epidemiological studies of vaccine efficacy are the accuracy and 'meaningfulness' of the parameters that they measure, and the difficulty in making useful comparisons between studies. Serological studies measure parameters that it is generally agreed do not correlate with immunological protection. Epidemiological studies measure reduced incidence and severity of disease as determined by variable case definitions, and they are subject to the influence of a multitude of confounding factors.

Epidemiological studies have advantages in that they can track large numbers of the population for a considerable length of time, and have the capacity to expose rare, unexpected and longer-term consequences of immunisation, both positive and negative. However, they limit their potential value when they fail to report, or even to record, sufficient detail on the study population, the background incidence of disease, case definitions and administration procedures.

It is well known that epidemiological studies in general are vulnerable to the influence of confounding factors, so placing a greater emphasis on fuller reporting of the circumstances of the study would facilitate recognition of the influence of these factors, help identify broader influences on the performance of vaccines and assist in revealing techniques to maximise the effectiveness of vaccine delivery programs.

CHAPTER 10

ADMINISTRATION OF VACCINES: APPLYING THE REMEDY

10.1 INTRODUCTION

"Administration" has two meanings: "application of remedies" and "management of public affairs" (Sykes 1976, p 14). Both these meanings are relevant to the process of achieving effective immunisation, and this chapter will look at "applying the remedy", that is, the practical considerations involved in the physical supply of vaccines to the target population. Chapter 13 will deal with the "management of public affairs" in relation to the funding and policy issues that determine the management and availability of this supply.

10.2 GETTING THE VACCINES TO THE PUBLIC

Once a vaccine has passed through the protracted and complicated stages of development, safety and efficacy trials and has been approved by the relevant government regulatory bodies such as the Federal Drug Administration in the USA

and the Therapeutic Goods Administration in Australia, it is still a complex process to deliver it appropriately to the public. The most relevant issues here are:

- reliable production and supply.
- cold-chain maintenance.
- storage.
- record keeping.
- injection techniques.
- knowledge and performance of general practitioners or other health workers.

10.3 RELIABLE PRODUCTION AND SUPPLY

Important considerations in the bulk production of vaccines are the potency, stability and availability of the manufactured product. Consistent potency in the production of vaccines is important to ensure they maintain optimal protective ability, and the stability of a vaccine is an important factor in determining its shelf-life under suitable storage conditions. Maintenance of adequate supply is important for consistent public use, and reserve stocks are important to buffer against unexpected outbreaks or accidents.

10.3.1 POTENCY

> Potency tests are essential for confirming that a particular batch of vaccine is acceptable with respect to its protective ability, measured in international units. It is especially important for live viral vaccines which deteriorate and lose their potency, when exposed to temperatures other than their recommended storage temperatures. (Saraswathy et al 1993, p 265)

Saraswathy et al (1993) found that 13% of vaccine batches exposed to temperatures outside the recommended range (2 - 8°C) had lost their potency. This was particularly the case if they had been exposed to higher temperatures for more than 24 hours.

There have been cases where, owing to problems in manufacture or storage, vaccines with inadequate potency have been injected into the target population, thus failing to provide them with the expected protection.

> In an analysis that compared mortality among children who seroconverted and children who failed to seroconvert, because they received an ineffective vaccine, mortality was 3 times higher for the non-seroconverters than for the seroconverters. (Aaby 1995, p 679)

However it is not just faults in manufacture or storage that contribute to loss of potency. This may also occur during the natural degradation of the product over time. The rate of degradation varies with different vaccine formulations.

10.3.2 STABILITY

Stability is the degree to which a vaccine retains its original characteristics over time when stored under the required conditions. A stable product will show few signs of degradation during its shelf-life, whereas an unstable product will show marked degradation in terms of loss of potency (death of live viruses, or changes in the composition of pathogen fragments) or reactions between components (Fenyves 1996).

Fenyves (1996) maintains that the regulations regarding stability are inadequate as they do not provide

> . . . guidance on how manufacturers and authorities should use the results of these studies in the establishment of shelf lives, or the acceptability limits for changes in product characteristics revealed by the studies. Limits, where specified, refer mainly to time intervals. (p 329)

There is, however, a need for “end-of-shelf-life specifications and for a justification of maximum acceptable levels of degradation products” (p330). This is because there is a big difference in quality between a product that has maintained a constant composition, and one that starts off with a very high virus concentration,

but degrades rapidly. By the end of the self-life they may have similar concentrations, but the second one will have varied considerably over the period of its shelf-life. It would have started out with a higher than necessary viral concentration, and ended with a significant proportion of degradation products. Both these factors may exacerbate adverse reactions.

There is also the consideration that the viral population is heterogenous, and if there is considerable degradation it is unlikely that the more resistant virus population left towards the end of the shelf-life would have the same characteristics as the initial virus population, thus introducing more variables and further potential for adverse reactions. There is evidence that this has occurred. Fenyves cites the case of a varicella vaccine that started at 10,000-15,000 pfu/dose and degraded to 1000 pfu/dose. The proportion of vaccine failures was higher than in children who did not receive a degraded product, and were also higher than in those children who received a varicella vaccine that was manufactured with a potency of 1,500-2,000 pfu/dose. This suggests “the potentially negative effects of an excess of inactivated material in unstable live vaccines” (1996, p 332).

Fenyves expresses his concern that:

> Accepting a stored product with extensively altered characteristics . . . is hardly compatible with a regulatory policy aimed at supporting and stimulating the improvement of vaccine quality. . . But our attempts to persuade WHO or EP [European Pharmacopoeia] expert groups to consider the problem of vaccine quality as a whole have been unsuccessful. (1996, p 332)

10.3.3. SUPPLY

Ensuring a constant and reliable supply of vaccines is no longer a simple matter of production schedules and reserve stocks. Behind it lies a complex mesh of political, funding, profitability and regulation issues that will be dealt with in more detail in Chapter 13. Mowery and Mitchell (1995) specifically discuss the situation in the

United States, but the situation is very similar in Australia and other developed nations.

The regulation of vaccine production has become costly to comply with and very complex. This has lead to many commercial producers of biological products ceasing to produce vaccines. In 1995 there were only four private USA owned firms in operation, and only two of those (Lederle-Praxis Biologicals and Merck & Company) were actively involved in the development of new vaccines. Since then there have been further mergers and take-overs, and now there are only two USA owned firms; Merk & Company and Wyeth Lederle Vaccines & Pediatrics (WHO 2002b). In Australia the only vaccine producer is CSL, and they are certified by the United Nations as producers of vaccines for DT (diphtheria/tetanus), TT (tetanus toxoid) and DTP (diphtheria/tetanus/whole cell pertussis) (WHO 2000b). Virtually all Australia's paediatric vaccines are imported from a range of suppliers.

The increased emphasis on patents and development of new research techniques has contributed to an increase in the number of joint development projects between licensed vaccine producers in the USA and overseas. This has also become necessary with the increased pressure to produce combination vaccines to simplify the childhood vaccination schedule, as companies may need to share antigens, patents and expertise.

Not only has vaccine production become concentrated amongst a few companies, but there is also the tendency for these companies to specialise in the production of only a small number of vaccines. In the United States these vaccines are licensed for production only at a particular plant. This jeopardises the security of supply there, as any interruptions to production in one plant cannot easily be made up elsewhere, even by the same company (Mowery & Mitchell 1995). This makes the

vaccine supply in the United States very vulnerable to interruption by, industrial accident, fire, industrial disputes with workers, or even terrorist attack.

Vaccines have a short shelf-life (usually two years) and companies maintain only limited amount of unpackaged product in reserve.

> Even under the most urgent circumstances, a large emergency vaccine order requires several weeks to process. (Vandermissen 1992, p 955)

Also, once supply had been reestablished,

> . . . catching up with the cohorts that missed key immunizations would be difficult and costly. Among other things, such a "catch-up" program would require excellent tracking data on child immunizations. The quality of the state-level tracking data on child immunizations, as well as the data used by states to forecast their demand for childhood vaccines, is often poor. (Mowery & Mitchell 1995, p 985)

This is as true for Australia as it is for the USA. Australia does have a centralised data-bank but records may be incomplete, and movement of the population and provision of vaccines by different providers often complicates the issue (McIntyre et al 1998; Bond, Nolan & Lester 1998).

Ironically, the situation for a highly regulated country such as the USA needing a large emergency supply of a particular vaccine is probably worse than that for a developing county. Developing countries can call on the resources of WHO or UNICEF, the Pan American Health Organization or similar bodies who procure vaccines from a range of approved suppliers around the world. The USA with stringent licensure and quality regulations would find it very hard to procure vaccines from any overseas sources and although:

> In an emergency, the USA government could approach UNICEF suppliers directly . . . this policy would still have problems related to FDA [Federal Drug Administration] licensure, the effect of such a large-volume purchase on UNICEF and PAHO and the difficulty a supplier would have in scaling-up to meet an emergency order of several million doses. (Mowery & Mitchell 1995, p 993)

It would also compromise the ability of these organizations to meet their commitments to the developing countries.

This has led the USA to look at the feasibility of providing for “surge supply”, but the options are costly and unclear. The USA created a stockpile in the 1980’s, but funding for this ceased in 1991. The existing six month supply has been maintained, but vaccines added to the schedule since then, such as acellular DTP, HBV or DTP/Hib are not covered. However:

> Stockpiling cannot resolve the consequences of a truly catastrophic supply interruption, such as the complete destruction of a sole-source production facility, because of the limited shelf life of vaccines and the length of time needed to license a new production plant. (Mowery & Mitchell 1996, p992)

Military facilities also exist for the production of vaccines, and have been considered as potential emergency back-up facilities. However, they are primarily geared towards producing vaccines against biological warfare agents under containment conditions, and are therefore unlikely to also be licensed to produce paediatric vaccines. Building a specialist facility is not only prohibitively costly, but the need for the continual production of test lots to maintain licensing means that “a licensed standby facility is feasible only if it is nothing of the kind” (Mowery & Mitchell 1996, p 995). Current public facilities have limited production capacity and would need time to scale up production to meet emergency needs, as well as extensive preparation over liability issues arising from the “sovereign immunity” of the USA government (Akula 2000).

There is no easy, cost effective solution to the problem of limited sources of supply in the USA The USA government has known for decades that in the event of any vaccine production facility having to close unexpectedly as a result of an industrial accident, or now with the potential for a terrorist attack, they would have enormous

difficulties maintaining supply. It may be a positive consequence of the recent terrorist attacks that the USA government finally seriously attempts to rectify this situation (Akula 2000).

In Australia there are at least two licensed overseas suppliers for each paediatric vaccine (NHMRC 2000a). Australian regulations maintain the flexibility to source alternate suppliers if there is an interruption or emergency situation (Misrachi A. 2001. Personal communication, 28 November). Suppliers maintain a small reserve stock, sufficient to comfortably meet demand and to cover minor eventualities such as a failed batch of vaccine. The importing agents, such as CSL also maintain a small reserve stock to meet fluctuations in demand or supply delays, and reserves equivalent to approximately 1-3 months are also held by the Health Departments of each State or Territory (Kaplan D & Misrachi A. 2001. Personal communication, 28 November). Australia therefore has a reasonable buffer-zone against a major interruption in production from any one of its main suppliers. It is also a significant consideration that our population is not as large as that of the USA and our regulations are not as unwieldy. Australia is therefore in a considerably better position than the USA to maintain reliable paediatric vaccine supply to its population.

10.4 COLD-CHAIN MAINTENANCE

The “cold-chain” is the term used for keeping the vaccines at the recommended refrigerated temperature (usually 2-8°C) throughout transportation and storage. This can realistically be seen as a challenge in developing countries with hot climates where the power supply may be unreliable, but it has proven to be fraught with difficulties even in the technologically sophisticated industrialised nations, and even in their most affluent suburban areas.

Freezing has an even more destructive effect on some vaccine formulations (particularly the live viral ones) than moderate heating. Some vaccine formulations are visibly altered after freezing (they look granular when shaken), but others show no apparent change (Health Canada 1995). It is therefore just as important to make sure that the vaccines do not become too cold, as it is to make sure they do not become too warm.

In very cold countries such as Canada, Russia and Scandinavia, this presents considerable problems, particularly as vaccines often have to be transported long distances. “Recent studies have highlighted major deficiencies in Canada with respect to the cold chain” (Health Canada 1995). They undertook special studies to determine the effectiveness of different strategies intended to extend the “warm-life” of their vaccine transportation facilities during winter, such as wrapping containers in newspaper and using tepid water packs instead of ice-packs.

Here in the warm climate of Australia it might seem contradictory that exposure to heat is not the primary problem, although it certainly does occur. This is because it is apparently all too easy to overcompensate for high temperatures during transportation and inadvertently freeze the vaccines, causing irreparable damage (NHMRC 2000a; Svanberg & Platt 1998). Vaccines may also freeze during storage if they are stored too close to the freezer compartment of a refrigerator, or near accumulated ice.

The most effective way to monitor the temperature exposure history of a batch of vaccines is to use various monitoring devices such as thermometers with minimum-maximum readings, continuous temperature recording devices (suitable for large shipments), dye containing capsules that rupture at a certain temperature, or “Tiny

Tag" electronic temperature monitors (Health Canada 1995, Svanberg & Platt 1998).

It is understandable that difficulties with temperature maintenance may be experienced during transportation, for example in the Hunter Area of New South Wales 25% of short journeys (up to four hours) and 80% of long journeys (4-24 hours) resulted in vaccines being exposed to temperatures over 10°C to "an unknown but negligible extent" (Miles 1993, p 169). However, it appears that

> the integrity of vaccines, already suspect at the beginning of the cold chain, would tend to be diminished to an unknown extent in refrigerators at the end of the cold chain. (Miles 1993, p 170)

This indicates that the greatest problems are found during storage – firstly at the State Vaccine Centres (the one referred to here is in New South Wales), but more particularly in the surgeries of providing doctors and community health centres.

In a survey of 59 vaccination centres (both doctors surgeries and community health centres) only 24% were storing vaccines correctly, that is, at a temperature between 2 and 8°C and in the correct location in the refrigerator. Community health centres performed slightly better, at 29%, than did doctors' surgeries at 22%. Vaccines were stored at both the wrong temperature and wrong location in 22% of centres, and 12 out of 13 of these were doctors' surgeries.

Eizenberg (1998) found similar problems in Victoria; Martin, Nayada & Kempe (1998) in South Australia; and Rixon, March & Holt (1994) in metropolitan Sydney NSW, although their findings cannot be directly compared because their criteria were different and they reported only on temperatures, not locations of storage. Of concern was their finding that:

> Despite providing education to vaccine providers over many decades few adhere to cold chain guidelines and recent temperature monitoring at

> vaccine provider sites show that vaccines are frequently stored below 0°C. (Martin, Nayada & Kempe 1998, p 31)

> A number of recent studies have highlighted a lack of appropriate cold chain provision in many general practices, and a lack of awareness that most vaccines are inactivated by freezing (Eizenberg 1998).

Martin, Nayada & Kempe (1998) also found that although they gave feedback and a

telephone interview aimed at correcting poor storage practices, despite initial

improvement, after 6 months most centres had reverted back to previous suboptimal practices, leaving only 52% of studied centres with optimal storage conditions.

These three studies highlight that there exists a considerable problem in maintaining vaccine integrity during transport and storage in well populated, well serviced areas. Ironically, despite these areas of Australia having a temperate climate, most temperature problems involved freezing rather than over-heating. This is caused partly by inadvertent overcompensation during transport, but by far the greater problem was inadequate storage at the provision centres. General practitioners and other health workers are often unaware of storage recommendations and the detrimental effects of freezing. Of more concern was the finding that after remedial intervention, practices declined rapidly to previous sub-optimal standards.

10.5 STOCK MAINTENANCE AND RECORD KEEPING

There are several issues related to maintaining adequate stocks of appropriate vaccines, and keeping accurate records on which vaccines have been administered

to each individual. These include labelling, combination vaccines, design of record forms and broken schedules.

10.5.2 LABELLING

It is important that the name given to a vaccine provides a clear indication of its nature, as there are now so many vaccines on the market there is increasing potential for confusion and mistakes in record keeping (Daum, Jain & Goldstein 1995). For example the recent use of Tetramune™ for a combination vaccine with Hib conjugate and DTP (HbOC/DTP) caused confusion as many health care workers were unaware of the components.

> A brand name like MMR®II, on the other hand, is substantially more informative and should increase the chances that the components of the vaccine are known to prescribing physicians and administrative personnel charged with rendering information on charting sheets and on vaccine cards. (Daum, Jain & Goldstein 1995, p 386)

This would help reduce the chance of errors both in vaccines that are given, and in record keeping.

Care taken to provide vaccines with clear and informative names may also help reduce the potential for mistakes such as the one that occurred in Ireland in the 1970's where children were administered with a bovine vaccine called Tribovax T instead of a whooping cough vaccine called Trivax (Payne 2001).

10.5.3 COMBINATION VACCINES

Although the increasing trend towards combination vaccines is admirably aimed at reducing the number of injections in the childhood vaccination schedule, it brings with it a host of practical problems that threaten to undermine this desired

simplicity. It may at first be thought that the use of combination vaccines would require vaccine providers to stock a smaller inventory, thus reducing costs. The reality is that providers would probably have to stock a larger range of products with greater expenses in acquisition and record keeping. For example providers may stock DTP, DTaP (with acellular pertussis), DTP/HbOC and MMR, but they also need to stock the components separately for use in specific situations.

DT is used when pertussis is contraindicated, tetanus may be administered separately after injury. There are situations where it may be appropriate to administer measles, mumps or rubella separately, although in Australia only rubella is available on its own. Australia has seven licensed Hib vaccines. PedvaxHIB is the current vaccine readily available for the paediatric schedule. If the schedule was started with another Hib vaccine that is different or unknown, it is recommended to complete the schedule with a total of three doses of any available Hib vaccine (NHMRC 2000a). This is despite a lack of research into the effects of varying the administered vaccine during a paediatric schedule. Presumably this recommendation has been made to simplify the stock requirements of both the Health Department and the vaccine providers, as completing a schedule with the same brand would require many brands to be stocked.

This is not a comprehensive list, but just from these few examples it can be seen that an inventory is complicated, rather than simplified, by combination vaccines. Record keeping is also complicated.

10.5.4 RECORD KEEPING

Accurate record keeping is essential to track the exact vaccine administered, the date and its batch number. This information is important for many reasons, but especially because:

- There are now many combination vaccines, and some have different administration schedules. The exact name of the vaccine must be recorded to facilitate this. In Australia there are seven licensed Hib vaccines, with two readily available. These are PedvaxHIB and Comvax with Hep B (NHMRC 2000a).
- In Australia a child's immunisation status must be declared on entry to childcare or school. If not immunised for a particular disease the child is required to stay home during an outbreak. Accurate records are required to prevent unnecessary exclusion (Public Health Act 1997#how to ref?).
- Records of vaccines administered are required to prevent giving repeat or unnecessary immunisations. It has been shown that even with a complete immunisation record 4% of children receive unnecessary repeat immunisations, and with incomplete records the figure climbs to 18%, thus wasting resources and risking increased adverse reactions (Murphy, Pastor & Medley 1997).
- The mobility of the population also demands accurate records, as many families will see more than one provider during the childhood schedule.
- Accurate records are also required to confirm, or refute, claims of adverse events. Batch numbers are particularly important here to determine if a particular batch is causing problems. Live viral vaccines such as whole cell pertussis and polio are difficult to produce consistently, and several cases of 'hot lots' or particularly toxic batches have been recorded (for example Payne 2001; Brandt 1979). However, only about 35-45% of general practitioners regularly record the batch number of a vaccine (Herceg, Johns & Longbottom 1997).

In Australia immunisation records are collected by the Australian Childhood Immunisation Register. This register records details of all children who have a Medicare number, that is about 98% of children under 12 months. The register depends on reports from providers, so their figures tend to be under-reported as some providers omit to report their activities, are unaware of the existence of the ACIR, or are reluctant to comply, though this situation has improved with the introduction of the financial incentives scheme in 1998 (McIntyre et al 1998).

Very basic problems arise with vaccination record cards when new vaccines, or new combinations are introduced and there is no appropriate space to mark them on the record cards. They are then often ambiguously noted, or left off (Daum, Jain & Goldstein 1995).

10.6 INJECTION TECHNIQUES

The site and method of injection of a vaccine makes a considerable difference to the efficacy of a vaccine and “plays an important role in avoiding adverse local reactions” (Relyveld et al 1998, p 1018). These factors play an important part in the long-term performance of a vaccine by ensuring that the antigens arrive in a manner to stimulate the most appropriate aspect of the immune system. For example:

> Later studies revealed a 26% vaccine failure rate among healthy mostly female health care workers immunized in the buttocks. Eventually it was discovered that investigators using the deltoid as compared to the buttocks for vaccination had reported significantly higher antibody response rates. The early trials failed to include data on the site of vaccine administration, needle length and injection technique, hampering comparison of immunogenicity results from study to study, and delaying identification of the factor responsible for poorer immunogenicity. (Poirier et al 1996, p 26)

However, the site and method of injection is rarely mentioned in efficacy studies despite the fact that:

> Different immunologic responses, titer heights and antibody kinetics were seen when hepatitis B vaccine was administered by different routes such as intradermally (i.d.), i.m. [intramuscularly] or subcutaneously, with anti-HBs levels eight to ten times higher following i.m. injection as compared to lower dose i.d. injection. (Poirier et al 1996, p 26)

There are several reasons for an increased rate of vaccine failure when the injection site is the buttocks. These include that the layers of fat there do not contain sufficient antigen-presenting cells that are necessary to initiate an immune response. Antigens may take longer to reach the circulation, resulting in a delay in presentation to T and B cells, and they may also be denatured by enzymes present in the fat tissue if they remain there for hours or days (Zuckerman 2000).

Serious local reactions are rare with intramuscular injections, but abscesses and granulomas may form with subcutaneous injections. Zuckerman (2000) suggests that health care workers be educated to use an appropriate needle length for the patient, as the amount of fat over the deltoid muscle of the upper arm varies considerably and is generally greater in females than in males. She found that a standard 16mm needle would not be sufficiently long to provide true intramuscular injection in 17% of men and 50% of women, and that a needle length of 25mm was more appropriate. The use of longer needles was also advocated by Diggle & Deeks (2000), who found that a 25mm needle produced significantly reduced rates of local reactions in children. Zuckerman also advocates the use of a wider bore needle as it "ensures that the vaccine is dissipated over a wider area" (2000, p 1237).

The NHMRC (2000a) recommendations on needle use are in line with these findings, although apparently in other countries such as Great Britain they are not so clearly spelt out (Diggle & Deeks 2000). To what extent Australian GPs adhere to these recommendations is an unknown factor, as it was not included as a question in any of the surveys of Australian GP immunisation performance reviewed in this thesis.

10.7 PROVIDER ACCESSIBILITY AND PERFORMANCE

10.7.1 PROVIDER ACCESSIBILITY

> Studies in the United States have shown that health care systems and immunisation provider services contain major barriers to childhood vaccination, including inaccessibility, insufficient staff, insufficient clinic hours, missed opportunities to vaccinate (i.e., not vaccinating children who present for another reason and are due or overdue for vaccination), and misconceptions about true and false contraindications to vaccination. (Herceg, Johns & Longbottom 1997, p 300)

There have been few studies of these factors in Australia, although Kilmartin et al (1998) found that most parents wished to have their children immunised, but factors such as provider accessibility and the pressures of living resulted in delayed or missed immunisations rather than apathy or unwillingness.

A study by Bond, Nolan & Lester (1998) found that offering home vaccination for children behind in their schedule was “effective, acceptable and cheap method of completing recommended vaccinations” (p 487). Their study confirms that part of the problem with staying up to date with the immunisation schedule is not reluctance on the part of the parents, but accessibility of the providers, or willingness of providers to give opportunistic immunisations.

> About a third of the parents of children behind in their vaccinations reported having recently consulted a doctor. In almost all of these cases the child could have been vaccinated at that time. (Bond, Nolan & Lester 1998, p 488)

The issue of opportunistic immunisations leads into the much larger issue of GP funding and time constraints, which will be dealt with in more detail in Chapter 14.

10.7.2 PROVIDER PERFORMANCE

The professional performance of GPs in relation to vaccine administration, varies considerably.

> One study showed that immunisation providers in Victoria were unaware of the NHMRC recommendations for diphtheria-tetanus-pertussis vaccine (DTP) and combined tetanus-tetanus (CDT) vaccine. Other studies found that GPs frequently do not follow the NHMRC recommendations for site of injection of vaccines and vaccine storage. (Herceg, Johns & Longbottom 1997, p 300)

The National Childhood Immunisation Program was started in 1994, and this involved a component of provider education, including a mailout of publications. A general improvement in GP performance was observed over two years, but there were still areas with consistently poor performance. For example opportunistic immunisation is always done by only about 30% of providers. This was one of the problems highlighted by the home vaccination study of Bond, Nolan & Lester (1998). Always recording the vaccine batch number is only done by 45% of providers, although that had improved from nearer to 30% before the education campaign.

Providers also showed poor knowledge of storage procedure. Only 27% of GPs had optimal storage practices (Bond, Nolan & Lester 1998; Rixon, March & Holt 1994). Vaccines were not always injected into the correct location, personal health records were not always completed, and advice on administration of paracetamol was given by only about 60% of GPs. The Australian Childhood Immunisation Register was not always notified, resulting in Bond, Nolan & Lester finding the usefulness of the Register "as a source of accurate information to be limited" (1998, p 488) although this situation has subsequently improved.

GPs showed variation in conforming to NHMRC recommendations for vaccination in relation to other health conditions and previous adverse reactions, and they tended to err on the conservative side. For example 90% would not give the vaccine if a child's temperature was greater than 37.5°C. The temperature limit has since been increased to 38.5°C (NHMRC 1997). However only 55-60% of GPs would give any vaccine if the child was on antibiotics, or give DTP again if the child had a temperature of 38°C after the last dose of DTP, despite the NHMRC handbook recommending that they do this.

So the performance of GPs in relation to immunisation is varied, with a significant proportion demonstrating inadequate knowledge of storage conditions, the effects of freezing on live viral vaccines, injection site, contraindications and NHMRC recommendations.

10.8 CONCLUSION

Once manufactured, providing vaccines to the public in optimal form provides challenges, and there are many areas with significant room for improvement. The most significant of these are maintaining vaccines at the correct temperature from production to use, and the performance of vaccine providers in terms of storage, availability, injection technique and knowledge of NHMRC recommendations. Chapters 13 & 15 will discuss the political and financial framework that underpins these issues.

SECTION THREE: IMMUNISATION AND SOCIAL POLICY

CHAPTER 11

IMMUNISATION AND HEALTH

11.1 INTRODUCTION

The World Health Organisation holds that:

> Health is a state of complete physical, mental, and social well-being, and not merely the absence of disease or injury. (WHO Declaration of Alma Ata 1978)

This definition, first put forward over 20 years ago, encompasses all aspects of the life of an individual. However, in the same time frame, the prevailing perception of health care has come to equate increasingly with medical care. Health care in Western society has been increasingly appropriated into the field of biomedical technology, to the extent that one is exhorted not to start a fitness program or a diet, without first gaining the approval of one's general practitioner and undergoing whatever medical tests are deemed appropriate. The locus of control over an individual's health has increasingly been moved away from the individual and into the domain of medical "experts" (Sax 1989).

It is interesting that this trend has not only occurred, but accelerated, since WHO first issued their broad ranging definition.

> Attempts to advance our understanding of this broad range of [health] determinants through research have, like the health care system itself, tended to focus their attention on the narrower concept of health: absence of disease or injury. This concept has the significant advantage that it can be represented through quantifiable and measurable phenomena: death or survival, the incidence or prevalence of particular morbid conditions. . . . Knowledge has increasingly become defined in terms of that (and only that) which emerges from the application of reductionist methods of investigation. . . The health care system has . . . become the conventional vehicle for the translation of such knowledge into the improvement of health: more and more powerful interventions, guided by better and better science. (Evans & Stoddart 1994, pp29-30)

Despite this, there is increasing evidence from a wide range of fields of investigation that the determinants of population and individual health are broad, predominately social in origin, intimately linked with the individual's sense of autonomy, value and connectedness with the community, and have profound and long term effects (Evans 1994).

11.2 INDIVIDUAL HEALTH AND SOCIAL STATUS

There is well documented evidence that general health and life expectancy correlates with all measured aspects of social status (Marmot 1986; Marmot, Kogevinas & Elston 1987). In the United Kingdom, the Black Report (Office of Population Census & Surveys 1972, in Evans, Barer & Marmor 1994) shows a correlation between lower socio-economic status and shorter life expectancy with a clear gradient to longer life expectancy following increase in social status. This gradient of correlation between the two variables has remained steady (or even increased) since the data were first collected in 1911, despite the fact that disease profiles and causes of death have changed significantly during this time. These

findings have been confirmed by similar studies in other countries, for example in Sweden (Vagero & Lundberg 1989), Australia (Turrell & Mathers 2000) and the USA (Krieger et al 1993).

> The diseases change, the gradient persists, again suggesting . . . an underlying factor, correlated with hierarchy and expressing itself through particular diseases. (Evans 1994, p 9)

Marmot studied ten thousand British public servants over two decades. He found that the (age-standardized) mortality, over a ten-year period, among males aged forty to sixty-four was about three and a half times as high for those in the clerical and manual grades, as in the senior administrative grades (Marmot & Theorell, 1988).

> There was an obvious *gradient* in mortality from top to bottom of the hierarchy. . . But in none of these groups are people impoverished or deprived (at least according to the common understanding of those concepts). (Evans 1994, p 5)

All are relatively well paid and in similar low risk office environments. There is therefore

> . . . *something* that powerfully influences health and that is correlated with hierarchy per se. It operates, not on some underprivileged minority of "them" over on the margin of society, to be spurned or cherished depending upon one's ideological affiliation, but on all of us. And its effects are *large*. (Evans 1994, p 7)

It is generally recognised that susceptibility to non-infectious and chronic diseases is determined by a wide range of environmental, genetic and personal life-style factors (Goldstein 2001; McMichael & Woodward 2001; Marks & McQueen 2001). That the same factors act as significant determinants of susceptibility to, and severity of, infectious disease is not generally so readily acknowledged (Evans

1994). The main context in which they are acknowledged as significant contributors to the burden and severity of disease is in relation to poverty.

> . . . a common interpretation of the correlation between socio-economic status and health – that "the poor" are deprived of some of the material conditions of good health, and suffer from poor diet, bad housing, exposure to violence, environmental pollutants, crowding, and infection – cannot explain [the observations of Marmot]. Indeed a focus on poverty can block progress in understanding, because it can be dismissive of further questions. (Evans 1994, p 5)

The accepted epidemiological view is that the lower socio-economic classes are more prone to disease because of lifestyle factors, such as poor nutrition, crowding, pollution, reduced access to health care etc. Morbidity and mortality are seen as a result of specific disease processes. Therefore if the action of the pathogens can be blocked with immunisation, then circulation of the pathogen within the community will be inhibited, and social class disease differentials can be reduced or eliminated. This approach has indeed been very successful in reducing the incidence of specific diseases in many populations.

> However, the historical data on health differentials by SES [socioeconomic status] have some implications that are inconsistent with this point of view, and that suggest that it has inherent limitations. (Hertzman, Frank & Evans 1994, p 80)

The studies cited above suggest that the factors responsible for the gradient of correlation between social status and health

> . . . have more subtle and complex effects than can be represented by a direct connection between particular "causal" variables and particular diseases . . . They suggest a more fundamental difference in "health" or "vitality" which expresses itself through risk gradients for most of whatever the currently predominant diseases might be. . . the real problem, and it *is* real, is that underlying state of vulnerability that is expressed in various diseases. Its sources and remedies might be a more ultimately fruitful focus of study. (Hertzman, Frank & Evans 1994, p 81)

In the last 50 years all industrialised nations have expanded their health care systems. With the exception of the United States, they have introduced systems to make health care available to the whole population regardless of ability to pay, and the use of health care has increased and become more equitable across social classes. However, the longitudinal data from the United Kingdom and other developed nations such as Canada show that the introduction of these systems has had no effect on the class-linked mortality gradient (Evans 1994).

The research of McKeown (1979) demonstrates that there were significant, continuous, and sustained reductions in mortality rates from infectious diseases before the advent of biomedical treatments for them. Both Marmot and McKeown found that improvements in health were not linked directly to medical care. The main causal factor was

> . . . improvement in economic position, but at least in Marmot's data it is clear that this is not as a result of an escape from poverty. And in each case, while people always die *of* something – this is both a cultural convention and a requirement of modern systems of vital statistics – there is reason to believe that the particular diseases recognized by medical science may not be the fundamental causes. (Evans 1994, p 13)

Similar studies on hierarchies in primate groups (Sapolsky 1990) and other studies on differential health and mortality by social class (Wilkins, Adams & Branker 1989; Wilkinson 1992) suggest that there exists some underlying, general causal process, correlated with hierarchy, which expresses itself through different diseases. The particular disease to which an individual succumbs may be an expression of, or a mechanism of, some other essential factor influencing health, rather than a primary factor itself.

On this evidence, the development and administration of vaccines to combat the incidence of particular infectious diseases within a population is still valid as a preventative health measure, provided its promotion is not regarded, as it currently tends to be, as a sufficient end in itself.

11.3 STRESS AS A FUNDAMENTAL CAUSAL FACTOR IN HEALTH STATUS

In studies on primates, animals lower in the social hierarchy not only have higher levels of chronic stress, but are less competent in coping with it (Sapolsky 1990). In studies designed to produce heart disease in primates with a high cholesterol diet, those primates lower in the social hierarchy developed more severe heart disease than those higher in the social hierarchy (Evans 1994). Studies conducted on many animals show that they generally "respond to a stressful environment that they cannot control with physiological changes that are harmful to their health" (Evans, Hodge & Pless 1994, p 182).

This observation, and that of increased morbidity and mortality in lower human social classes, may be explained as a result of reduced function of the immune system.

> Observations of reduced immune function in students during exam time, accountants at income tax time, and people who have lost a spouse now begin to fit into the story . . . If immune status is compromised by stressful events, then this may be an alternative pathway through which social status can have generalized health effects. (Evans 1994, pp14-15)

It has been shown that lower status workers are generally less effective in coping with stress, and with turning off the stress response when they return home (Sapolsky 1990).

> Is it because people in the lower ranks are under greater stress, or because they are in themselves less able to bear the strain that follows from stress,

> or because their environments, at work, or at home, do not provide the supports that would permit them to transfer some of the strain? These possibilities are, of course, interactive, not mutually exclusive. (Evans 1994, p 22)

There is a substantial body of literature that documents the role of the environment in helping the individual cope with stress. There are strong correlations between mortality and social support networks, especially family and friends (House, Landis & Umberson 1988). There is also plenty of documentation to show that work that is unpredictable, and where the individual has no autonomy or control in their responses, or that is repetitive and underutilizes the individual's abilities, is associated with higher rates of morbidity and mortality (eg Karasek & Theorell 1990; Johnson & Johansson 1991). The lower status workers in Marmot's (1986) study were far more likely to report underutilizing their abilities, having no sense of control, and finding their work dull, than the higher status workers.

> Such findings suggest, plausibly, that it may be the quality of the "microenvironment" both social and physical, which is critical to health, rather than some mechanical connection between "health and wealth". (Evans 1994, p 22)

In fact it appears to be the equality of income distribution within a society, and the quality of social policy, that has a greater impact than simply average income per capita (Wilkinson 1992). This will be discussed in more detail in Chapter 12.

11.4 SOME IMPLICATIONS FOR IMMUNISATION

The correlation of morbidity and mortality with social class has implications for immunisation that are as yet unexplored in the literature. The questions it raises include the following:

11.1.1 VACCINE FAILURE

Are there predictable social determinants of vaccine failure? The immunological literature on vaccine failure (see for example: Black et al 1991; Booy et al 1997; Edmonson et al 1990; Longini 1993; Nkowane et al 1987) restricts itself to merely reporting percentage incidents. If any hypothesis is proposed as an explanation, it is limited only to a consideration of vaccine potency, efficacy, dose and scheduling.

On one level individual variation in immune response is taken for granted. That is, a certain proportion of vaccine failures are expected and used to calculate vaccine efficacy. For example:

> Of 164 reports of invasive infection between Oct 1. 1992, and Oct 1. 1995, 43 were considered true vaccine failures. The estimated overall efficacy for three doses of PRP-T was 98.1% (95% CI 97.3-98.7%). . . A true vaccine failure was defined as invasive Hib disease occurring more than 2 weeks after a single dose of vaccine given to an infant of more than 1 year; or more than 1 week after at least two doses had been given (at least 1 month apart) to a child younger than 1 year. (Booy et al 1997, pp 1197-98)

However these reports are strikingly lacking in any information, statistical or anecdotal of any personal or social factors that may have some bearing on the circumstances under which the child was immunised. There is no consideration given even to purely medical information, such as: whether the child's temperature was above normal at the time of vaccination; whether they were suffering from any other illness or medical condition, or on any medication at the time of vaccination; whether they were about to undergo surgery, dentistry or any other medical procedure. That is, there is no reporting on any physical factors that may have led to reduced or altered immune function.

These studies also fail to provide information about socio-economic status, age, income, or employment of parents. The current family situation is another large

factor in a child's life that may impact on immune function. Given that immune function is suppressed in stressful situations, a serious parental argument just prior to immunisation may have a significant effect on the child's ability to respond appropriately to the vaccine. These factors are all worthy of formal consideration. Studies to determine vaccine efficacy would be far more informative, and of use in formulating policy for vaccine administration, if even some of these factors were included for consideration. Consideration of most of these factors can be accomplished by the inclusion in the studies of a simple questionnaire.

11.1.2 OUTBREAKS OF DISEASE IN VACCINATED POPULATIONS

There is well documented evidence of outbreaks of vaccine preventable infectious diseases in highly vaccinated populations, see for example the account of an outbreak of measles in an Australian high school by Herceg, Pessaris & Mead (1994). Once again, discussion is limited to number of cases, percentage of population immunised and estimates of vaccine efficacy:

> Overall, 95 percent of children had been immunised. The efficacy for all measles vaccines was estimated to be 90 per cent . . . (Herceg, Pessaris & Mead 1994, p 249)

These reports are devoid of any consideration of the generic social situation surrounding the community involved in the outbreak. Factors to consider might include whether there have been any recent situations that have increased the stress levels of the community in a way that may have contributed to reduced immunity or whether there have been any recent changes in government policy affecting employment, benefits or access to health care.

An example that supports this approach is provided by Lithuania and Russia in the early 1990's. Both nations used the same Russian manufactured vaccines and

implemented very similar immunisation schedules. However, after the dismantling of the Soviet Union in 1991, Russia experienced sudden and severe epidemics of vaccine preventable infectious diseases such as diphtheria, tetanus, measles and whooping cough (Kim et al 2001), whereas Lithuania did not (Rix et al 1994). For example, the incidence of diphtheria in Russian reached a rate of 26.6 per 100 000 of population (Field, Kotz & Bukhman 2000), whereas in Lithuania the incidence of cases was 0.03-1.15 per 100 000 of population. Most of these cases were a result of low immunity and contact with infected Russians (Usonis et al 2000). The Baltic States did report a slight decline in general population health, particularly womens' health, as a result of the uncertainty in the change to a market economy, but to nowhere near the same extent as that reported by Russia (Nadisauskiene & Padaiga 2000). Amongst the complex social and economic factors in the equation lies the simple fact that Lithuania, and the other Baltic States, had long desired independence and were pleased with the change in political status, whereas Russia lost its dominant status and its citizens lost the security of the socialist state. It is possible that a fundamental cause in the epidemics was the stress, insecurity and low morale experienced by the Russian population.

> . . . factors in the social environment, external to the health care system, exert a major and potentially modifiable influence on the health of populations, through biological channels that are just now beginning to be understood. (Evans 1994, p 23)

11.1.3 HERD IMMUNITY

Put very simply, herd immunity is the notion that:

> If enough people in the community are immunised, the infection can no longer be spread from person to person and the disease dies out altogether. (Commonwealth Department of Health 1995, p 10)

The Australian Childhood Immunisation Charter 1998-2000 states the goals of:

- greater than 95% coverage of children of school entry age for diphtheria, tetanus, pertussis, polio, measles, mumps, Hib and rubella.
- greater than 95% coverage of girls and boys by 17 years of age for measles, mumps and rubella . . .

(from Moore 1998, p2)

The reason why vaccination rates of 95% are sought is because diseases such as measles and pertussis are "highly infectious and often misdiagnosed" (Anon 1983).

Actual rates of immunisation in Australia are close to this. About 92% of children aged 3 months to 6 years are fully immunised for DTP, about 85% for MMR and 76% for Hib (ABS 1995, p 4).

It is traditional, in the case of an outbreak of vaccine preventable infectious disease, to blame inadequate herd immunity. In the words of William Osler in 1901:

> To be efficient, vaccination must be carried out systematically . . . the difficulty arises from the constant presence of an unvaccinated remnant, by which the disease is kept alive. (Preda 1996 in Clearihan, p 901)

And again more recently:

> It is widely accepted that universal infant immunisation is the key to disease prevention and control of infections. (Meheus 1996 in Clearihan, p 901)

Inadequate herd immunity continues to be cited as a cause even when immunisation rates are high, and the disease is also being spread by vaccinated children (for example: Briss et al 1994; Edmonson et al 1990; Herceg, Pessarias &

Mead 1994; Hutchins et al 1990; Matson et al 1993; Nkowane et al 1987; Shvartzman et al 1991; Sutter et al 1991).

Herd immunity sounds convincing in theory, but in reality is a limited concept, as outbreaks of vaccine preventable disease still occur in highly vaccinated populations (eg Herceg, Pessaris & Mead1994; Osaki et al 2000; Sutter RW et al 1991). In the light of the broad ranging evidence on population health presented in this chapter, a more useful concept suggested by this thesis, would be population resilience.

Some population characteristics, for example high levels of maternal education, are consistently associated with good population health even at low levels of average income (Evans 1994). Populations of some less developed nations are much healthier than those in others with similar per capita incomes. For example, the infant mortality rate for Costa Rica and Sri Lanka is about 64 per 1000 live births and life expectancy is 61 years, whereas for Afghanistan and Morocco the infant mortality rate is about 173 per 1000 and life expectancy is 45, yet all these countries have similar per capita incomes (Caldwell 1986).

> The difference seems to be that the countries with better health status have placed a greater emphasis on the importance of women and children in their culture and social environment, and in their social policies. . . These examples show that major shifts in the health status of whole populations over time do not necessarily depend upon the implementation of public health or medical control measures against specific diseases. They point instead to a profound linkage between health and the social environment, including the levels and distribution of prosperity in a society. (Hertzman, Frank & Evans 1994, pp 70-71)

In this context the recent debate in Australia over paid and extended maternity leave entitlements becomes not just a matter relating to economic and social policy, but should also be debated on the basis that it is an important health

measure. It would provide greater security and control for women with young babies during the time when the babies are most vulnerable and most susceptible to infectious diseases because their immunisation schedules are not complete. In a similar manner, calls for a review of the complete package of government family support can be justified as a health measure with long-term consequences for the health of both parents and children. The development and maintenance of herd immunity, or more appropriately population resilience, will benefit from being seen as a policy issue that reaches much further than immunisation rates.

11.5 ADOPTING A BROADER APPROACH TO POPULATION HEALTH

The evidence of broader causal factors contributing to disease encompasses social status, stress, social relationships or their absence, feelings of self-esteem and self-worth, hierarchical position and feelings of control or powerlessness. These factors "appear to have health implications quite independent of conventional risk factors" (Evans & Stoddart 1994, p 45). These underlying factors remain constant and have serious implications for the formulation of health policy. The research in this area clearly gives the message that:

> Disease specific policy responses – through health care or otherwise – may not reach deeply enough to have much effect. Even if one "disease" is "cured" another will take its place. (Evans & Stoddart 1994, p 46)

The challenge is to broaden the notion of health care and its supporting policy beyond the limitations of the biomedical model. If too great a proportion of national income is spent on biomedical care, an ironical result can be a reduction in national health status. This is because there is then not enough being spent on other health enhancing activities and facilities such as improving the education system (Evans & Stoddart 1994). A holistic approach to population health is required.

Immunisation as a preventative measure for infectious diseases needs, therefore to be kept in perspective. It is a valuable resource. It is very observable, and therefore reassuring, but it is not the only means, or even maybe, the most effective means of reducing the incidence of infectious diseases in a population. Given that to date the research on the effectiveness of immunisation has been conducted within the narrow parameters of the biomedical perspective, there is much scope for both scientific and epidemiological research into the broader, social determinants of susceptibility and resistance of both individuals and populations to infectious disease.

CHAPTER 12

HEALTH CARE, IMMUNISATION AND AN INTERNATIONAL PERSPECTIVE

12.1 INTRODUCTION

The issues that were identified in Chapter 11 as operating on a national level have also been observed to act in a similar manner on an international level. There exists a correlation between the general health status of a nation's population and that nation's status in the global community. Global policy on economic, ecological and social issues can be shown to have long lasting and broad ranging effects on the health status of nations as a whole.

12.2 INTERNATIONAL STATUS AND NATIONAL HEALTH

The social status/health correlation discussed in Chapter 11 that is observable at a class level within a nation, is also observable at an international level, and is liable to alter in line with a change in economic or political status. One indicator of the ability of populations as a whole to experience a fairly rapid change in health status is the observation that migrant populations rapidly take on the disease profile and life expectancy of the country to which they move (Doll & Peto 1981).

The recent increase in life expectancy in Japan is more closely correlated to its rise in economic status after World War Two than it is to any increase in health care (Marmor 1992). Indeed the Japanese spend the lowest proportion of national income on their health care in the industrialized world, and the majority of the population live in cities where the life-style tends to be counter to the conditions normally accepted for optimum health, that is, it is generally crowded, stressful and polluted (Ingelhart 1988). However,

> . . . *something* lies behind the undeniable increase in their longevity. Unique features of the Japanese diet, or of social structure, have received considerable attention, but these of course have *not* changed rapidly over the last thirty years. What *has* changed is the hierarchical position of Japanese society as a whole relative to the rest of the world. (Evans 1994, p 18)

However, recently Japan has been experiencing an economic recession, and in line with this there have been reported increases in the rates of vaccine preventable infectious diseases such as measles (Ohsaki et al 2000).

12.3 HEALTH AND CHANGE IN RUSSIA

Russia acts as an example of how a well-developed nation can experience a sudden reduction in health status as a consequence of economic turmoil, unequal distribution of resources and a generic state of population stress and insecurity. As discussed in Section 11.4.2, Russia experienced a dramatic reduction in health status immediately following the disbanding of the Soviet Union. The mortality rate was a steady 10-11 per thousand live births during the 1980's, but rapidly increased to 15.7 per thousand between 1991-94. The birth rate dropped by 45% between 1987 and 1993. In 1992, the first year of Russia's independence, what had been a healthy rate of population increase suddenly turned into a decrease.

> Since 1993, deaths in Russia have exceeded births by five to six per 1000, a demographic pattern usually seen only in times of war, famine or plague. (Field, Kotz & Bukhman 2001, p 158)

Amongst a plethora of health statistics that give cause for concern are a marked increase in adult male mortality rates due to alcoholism, suicide and accidents. Life expectancy for adult males in Russia is now 57 years, placing it below a number of impoverished Third World nations such as Costa Rica and Sri Lanka (Caldwell 1986; Field, Kotz & Bukhman; Notzon et al 1998). These causes of mortality are widely accepted as indicators of a population under stress, however the epidemics of vaccine preventable diseases can also usefully be seen in the same light.

> Uncontrolled environmental pollution and unhealthy life-styles are commonly cited explanations, and are certainly part of the explanation. But the observation is at least consistent with the hypothesis of a relationship between collective self-esteem and health – a relationship that could be expressed through unhealthy life-styles. (Evans & Stoddart 1994).

The incidence of diphtheria, which has almost disappeared from most wealthy countries, rose from 0.4 cases per 100 000 of population in 1989 to 10.3 per 100 000 in 1993 and 26.6 per 100 000 in 1994. This rate is in excess of most impoverished nations. In 1992-3 the incidence of measles, which had been stable for some years suddenly rose by 300%, and the incidence of whooping cough rose by 63%. In the same period deaths from tuberculosis, which had been falling until 1990 rose by 15% in 1992, this included a rise in the number of children suffering from tuberculosis, and also an increase in the incidence of multi-drug resistant strains. Other infectious diseases that rose in incidence at the same time include hepatitis B, cholera, typhoid, anthrax, salmonellosis and syphilis (Field, Kotz & Bukhman 2000).

A high percentage of those affected by the epidemics of vaccine preventable diseases, and particularly diphtheria, had been vaccinated (Vitek et al 1999). Literature on these outbreaks focuses on the issue of immunisation and its apparent failure to provide protection. The literature is concentrated around issues of standards of vaccine production, titres and schedules of doses, and primary and secondary vaccine failure (Niyazmatov et al 2000), where primary failure is when the vaccine does not "take" or elicit a response when initially administered, and secondary failure is waning immunity.

There is minimal discussion of the fact that the outbreak coincided with the disbanding of the Soviet Union in 1991, the dismantling of the socialist state and the rapid conversion of the economy in line with neo-liberal policies. While the epidemic may have been linked to specific physical circumstances following the political change, the general milieu and population morale were not generally viewed as causal factors in the epidemic. However,

> Several potential causal links can be postulated for the "coincidence" in timing between the implementation of neoliberal strategy and the health crisis. The following consequences of neoliberal strategy . . . are likely to have had direct effects on health: 1) the sudden impoverishment of a large part of the population; 2) the large increase in inequality; 3) the loss of security due to the dismantling of the social safety net; 4) the decline in public order; and 5) the reduced quality and availability of health care. To this list should be added the "shock" effect of the sudden disappearance of the economic, political, and cultural institutions that had organized life in Russia until 1992 – that is, the dissolution of the world to which people had become accustomed. (Field, Kotz & Bukhman 2000, p 168)

> In Russia, dismantling the pre-existing economic system before anything had been created to take its place has predictably produced chaos, depression, impoverishment, sudden enrichment of the few at the expense of the majority, and a collapse of public order. (Field Kotz & Bukhman 2000, p 166)

> . . . the everyday lives of Russians are still insecure, unpredictable, and filled with hardship. . . recent economic, political, and social turbulence has exacerbated Russia's health problems . . . (LeSar et al 2001, p 72)

The influence of generic social situations on outbreaks of vaccine preventable infectious disease in populations with a reasonable degree of vaccine coverage, is a fruitful area of research that the biomedical model tends to inhibit, as explanations along the lines of the circulation of virulent and/or highly contagious strains of a particular pathogen, primary and secondary vaccine failure and inadequacy of vaccine coverage are generally accepted as sufficient.

12.4 INTERNATIONAL POLICY AND HEALTH IN POORER NATIONS

The equality of income distribution, and quality of social policy within nations has a profound effect on health outcomes (Wilkinson 1992), and the same principles can be seen to operate on an international level. The values and quality of global economic policy exerted by the wealthier nations over the poorer ones through the vehicles of International Financial Institutions (IFIs) such as the World Bank, the International Monetary Fund (IMF), and international commercial banks and insurance agencies, have had a profound and lasting effect on the health status of the populations of the poorer countries,

The majority of the nations designated as "developing" service substantial debts on loans for development regulated by International Financial Institutions such as the World Bank and the International Monetary Fund. In the late 1970's to mid 1980's there was an international "Debt Crisis" when it became apparent that many heavily indebted developing nations were "unable to continue making payments on their debts to commercial banks in wealthy countries" (Gershman & Irwin 2000, p 20).

> "Solving" the Debt Crisis involved imposing structural adjustment programs (SAPs) on the economies of debtor countries, thus allowing these economies to "return to growth" and most importantly, to continue making interest payments on their foreign loans. (Gershman & Irwin 2000, p 20)

These structural adjustment programs are based on the three economic tenets of

1) Privatization: reducing the role of the state relative to the market in the economy.
2) Liberalization: enhancing economic efficiency by allowing prices to be determined by market forces, such as exchange rates, interest rates and real wages.
3) Deregulation: integrate the national economy into the world economy by lifting barriers to trade and investment.

   (from Woodward 1992).

In many of these countries the interest rates paid on these loans is in excess of national spending on health care, for example:

- In Africa as a whole, governments transfer to northern creditors four times more in debt payments than they spend on the health and education of their citizens.
- In Mozambique, debt servicing for 1996 absorbed twice the amount allocated to the combined current budgets for health and education. This, in a country where one-quarter of all children die before the age of five as a result of infectious disease, and where two-thirds of the population is illiterate.
- In Niger, the country at the bottom of the UNDP's Human Development Index, life expectancy averages 47 years and only 14 percent of the population is literate, but debt servicing absorbs more than the combined budgets for health and education.

(Gershman & Irwin 2000, p 25)

> The World Bank has recognized that health measures such as the control of communicable diseases and public health education are basic public goods that will likely be undersupplied by the market. Yet despite this recognition of the market's failure to guarantee health care, the World Bank still promotes market driven policies, such as cost recovery. (Gershman & Irwin 2000, p 30)

Indeed, the World Bank still encourages these impoverished nations to withdraw state support and implement user pays systems for health care to enable them to service their debts. In some of these nations health expenditure is as little as 2% of a generally low Gross Domestic Product (Schoepf, Schoepf & Millen 2000), whereas Australia, which has a higher GDP than most of these nations spends a consistent 8-8.5% on national health (Hall 1999). Despite acknowledging the health problems that have arisen as a result of these policies, and the existence of reputable literature and research that testifies to their adverse outcomes, the World Bank has not altered its user-pays policy for health care (Schoepf, Schoepf & Millen 2000).

Much of Africa's rural population lives in remote areas in conditions of absolute poverty, that is, their income is inadequate even to cover basic food requirements (Millen, Irwin & Kim 2001). It could therefore be argued that sufficient government funds should be spent to ensure they have adequate access to health services, and indeed, during the 1960's to 1970's this is what was done, with attendant improvements in general health status.

However starting in the 1980's, the reduction of the role of the state in provision of essential services and the implementation of user pays schemes has resulted in severe disadvantage to the poorest members of these societies. In countries where much of the population is either unemployed, or earns only a few cents a day and therefore has insufficient income for adequate food, clothing or shelter, *any* cost for health care places it beyond their reach.

> More than 30 countries in Africa operate national cost-recovery systems in health-care. Not coincidentally, in large areas of sub-Saharan Africa, the quality

of care as measured by attendance levels in hospitals and clinics has been falling since the late 1980's. Recent studies in Zaire, Nigeria, and Zimbabwe all found that previously stable attendance rates at medical facilities plummeted after the introduction of user fees (Gershman & Irwin 2000).

> User charges for health services are being increasingly adopted by developing countries, often at the behest of the World Bank or International Monetary Fund. Unfortunately, the arguments in favour of user fees are not supported by empirical data. (Moses et al 2000, p 466)

When South Africa recently removed the user fees from health care, attendance rates, particularly for maternal, immunisation and other preventative health measures increased back to previous levels immediately (Simon 1997; U.S. Civil Society Coalition 2002).

The imposition of user fees, however, are not the only barriers confronting the poor who seek biomedical health care, a person's ability to reach a health-care facility, to be treated by a health-care provider, or to obtain needed medicine is dependent on many factors, including proximity to the facility, transportation costs, ability to pay service and medicine fees, and sociocultural factors such as language, class, and gender (Moses et al 1992).

In fact in many hospitals and clinics in African countries, inpatients must bring all their own supplies, including medicines, disinfectants and bedding and a relative or friend (often a child) to care and cook for them. If they are unable to provide for themselves they either go without or are denied admittance (Millen in Kim et al 2000).

One reason why this situation has been allowed to develop and persist is that these poorest members of society lack any political power. They are generally illiterate, live in remote areas, find transport and communication with other groups difficult and prohibitively expensive and are therefore unable to exert sufficient influence over the political and economic decisions that affect their lives.

> . . . governments found it expedient to cut expenditures on services for those with little political influence. Public health outlays for the poor all too often provide such a strategy, where budget austerities are attended by only minimal political risks. As a result, public hospitals and clinics in many parts of Africa are now desperately under-staffed and poorly equipped. Budget compression under SAP's reduced support for health in most countries to about 2 percent of GDP. (Schoepf, Schoepf & Millen 2001, p 109)

The situation in Latin America is very similar, and the following example from Peru demonstrates how the imposition of user fees on poor populations may have far reaching and unpredicted effects that undermine the provision of important preventative health measures, and leads to lower health outcomes for the whole community. In the early 1990's, dramatic economic measures were taken to service Peru's international loans. These had a serious effect on the health of the poor in that nation.

> Sharply declining health indicators in the early 1990's suggested to many that the increasing inequality of economic distribution under [President] Fujumori had contributed to a parallel disparity in susceptibility to disease. A survey of 400 low income households between June and November 1990 showed that rates of sickness increased 20.6 percent, while spending on the purchase of medicine fell 50.7 percent in the same period. (Kim, Shakow et al 2000, p 138)

In the mid 1990's, many families in Peru earned less than $5 a week. Although tuberculosis check-ups and treatment were free, a definitive test for the disease carried a charge of $4 for saline, gloves and other equipment not covered by the program. This put it beyond the financial reach of many workers, let alone those who were unemployed. The result is that many cases of tuberculosis went

undiagnosed and therefore remained contagious in the community despite the existence of a free treatment program (Kim, Shakow et al 2000). This problem was exacerbated because the BCG vaccine “remains a highly controversial method of preventing tuberculosis” owing to the great range in estimates of its efficacy (Clemens, Chuong & Feinstein 1983, p 2362).

In many poor nations in Africa and South America, the World Health Organisation has expended much money and effort on its Expanded Program on Immunisation, the success of which has been widely publicized. Since it started in 1974, many poorer countries have certainly needed support for their health sectors, and protection for their population against the frequent outbreaks of many infectious diseases. However, although it may be argued that immunisation has considerably reduced the incidence of vaccine preventable diseases in these poorer countries, in the long term it has proven ineffective in preventing major outbreaks of infectious diseases. This is because the real cause of the considerable health problems of these nations lie not in the circulation of pathogens, but in the economic situation of the population.

Although the following quote is in reference to African nations, the case is similar for many other impoverished nations:

> The cumulative consequences of the slave trade, violent colonial conquest and the brutal extraction of natural resources by imperial powers created an enduring legacy of structural imbalances: entrenched asymmetries between Africa and the West, and between rich and poor within Africa. In this perspective, economic recovery depends on transformation of distorted production and power structures and on reversing Africa’s role in the world economy as a supplier of cheap labour and cheap raw materials.
>
> Such critiques, however, were either systematically ignored or dismissed as “ideological” by the Washington Consensus [an influential group of neo-classical economists]. (Schoepf, Schoepf & Millen 2000, p 91)

Even though there exists evidence equating income inequity with poor population health, little has been done to address this situation even in the nations where the situation is most extreme (Millen, Irwin & Kim 2000b).

On a global level the connection between national status and health outcomes can usefully be factored into the health policy of organisations such as WHO, UNICEF and various non-government aid agencies. If any nation is experiencing epidemics of vaccine preventable infectious diseases, as well as other systemic health problems, then it must be recognised that it is not a sufficient measure to run a nationwide immunisation campaign. This is despite the fact that there is now considerable international expertise in doing this, usually a high degree of international, government and community support, and that it is a very visible way of looking as though something is being done to improve the situation. Ultimately the situation will only really improve when the entire economic, ecologic and social situation of that nation is constructively and sensitively addressed to bring about genuine and lasting improvements in population health. Until then, current disease prevention efforts, such as immunisation, are limited to bandaid status, as the malnutrition, chronic stresses and immune suppression experienced by the disadvantaged members of that society will simply find another means of expression.

12.5 NATIONAL HEALTH AND STATE INVOLVEMENT IN CUBA

Cuba is a third world nation with a first world health profile. It has an economic profile similar to many of the poorer nations in Latin America, for example the GDP per capita of Cuba is $3000, placing it at the lower end of the scale in company with Bolivia $2598 and Guatemala $3208, whereas Mexico has a GDP of $7384, Chile $9129 and the United States is $26 980. In addition to this, it bears the added

handicap of trade embargoes and sanctions enforced by its large and powerful neighbour the United States, in protest against the Cuban communist government lead by Fidel Castro. Since 1992 the US trade embargo has explicitly included food and medicine.

However, Cuba's health profile is that of an affluent industrial nation. On most important measures it is very similar to the United States. In fact the infant mortality rate has continued to decline, and the life expectancy continue to increase despite the very real hardships imposed by the US trade embargoes.

Health Measure	Cuba	United States	Guatemala	Bolivia
GDP per capita	3000	26 980	3208	2598
Number of people per physician	275	421	3999	2348
Life expectancy at birth in years M/F	74/78	74/80	63/68	59/62
Infant mortality rate per 1000 live births	9	8	45	71

(figures from Chomsky 2000, pp 334-36)

The reason for this is the policy approach that the Cuban government has taken towards the health of its people. The fundamental difference is that the government sees the health of the people to be a primary responsibility of the state. It also sees health as a broad ranging social issue that includes health-care delivery but is far from limited to it.

> Thus the state is responsible not only for building, maintaining, and ensuring universal access to doctors, clinics, and hospitals, but also for guaranteeing and sustaining the social conditions necessary for health: universal access to education, food and employment. (Chomsky 2000, p 333)

This holistic concept of health is seen as a cooperative national project with a high degree of community involvement. The result of these policies has been the development of a health-care delivery system that provides both public and preventative health and universally accessible hospital care with technology equivalent to most industrialized nations.

A notable characteristic of the Cuban health-care system is the spread of resources that ensures regional equality.

> Over the last 15 years, the government has invested considerable effort in mitigating social and health discrepancies among regions of the country. Although income levels among provinces still vary, Cubans from every province, even the poorest, are well provided for in terms of health. (Chomsky 2000, p 335)

This has been possible because the state control of the economy has meant that resources can be allocated, distributed and re-distributed according to ongoing assessments of need. The Pan American Health Organisation has noted that the nations sustained good health was a result of:

> . . . the great capacity and effectiveness of the National Health System; the high cultural level of the Cuban people and their active participation in social and health programs . . . the health consciousness of the population, who consider health one of the country's greatest social triumphs; and Cuba's social and health policies, which have maintained their priorities despite the current difficult conditions. (PAHO 1994, pp153-54)

In 1992 there began an epidemic of optic and peripheral neuropathy. By 1993 there were 3 000-4 000 new cases per week. The government quickly devoted resources to identify the problem. Vitamin deficiencies, particularly vitamin B deficiency was identified as a risk factor, although the exact causes were not known. The government obtained the necessary equipment to manufacture vitamin supplements, at considerable expense from non-US markets, and these

supplements were distributed to all citizens. Most responded well to the supplements and there were no fatalities, the epidemic declined sharply. The government has maintained the supply of vitamins to the population throughout the time of deprivation caused by the US embargoes on food and medicine. A WHO official noted that:

> I found profound injustice in the occurrence of this huge epidemic of nutritional cause in a population not at war. Although the US economic embargo against Cuba was not the primary cause of this epidemic, it certainly contributed to its development, complicated its investigation and treatment, and continues to hamper its prevention. (Roman in Chomsky 2000, p 349)

Cuba has not had major epidemics of vaccine preventable infectious diseases. This places it in stark contrast firstly to Russia where the policy has been to withdraw state support for health, and to other impoverished nations who have easier access to the vaccines and drugs produced by the US and other major suppliers, but who have also withdrawn much of their state support for health measures in line with the neo-liberal policies imposed on them by the International Financial Institutions.

This discussion of Cuba is not intended to act as a support for communism as a political ideology, but intended to show that the increasing drive for privatization of the health sector in industrialized nations, and the very narrow view of health issues promoted by the biomedical perspective, are not the only options, nor even the most effective ones.

12.6 CONCLUSION

It has been shown that national status in the global community and equality of income distribution within that nation are significant determinants of population health in general, including rates of vaccine preventable infectious diseases. Therefore a dominant biomedical model of disease, which focuses on the circulation of pathogens within the community as the primary cause of infectious disease, and immunisation as its primary preventative measure, may well be counterproductive. This is because it may be contributing to an international sense that sufficient is being done to combat outbreaks of infectious diseases in the poorer nations, when in fact the ultimate cause of these outbreaks is systemic economic imbalance and the neoliberal policies imposed on these nations as part of the restructuring of their economies to ensure their capacity to service loans to international financial institutions.

The range of related factors considered by the biomedical community as explanations for outbreaks of vaccine preventable infectious diseases is very narrow and hugely inadequate. This limitation in perspective is inhibiting further research into important economic and social issues that have been proven to have profound and effective long-term repercussions for the health of populations as a whole.

CHAPTER 13

ADMINISTRATION OF VACCINES: POLICY AND FUNDING

13.1 INTRODUCTION

When it comes to delivering effective vaccines to the public,

> . . . political, social and public policy issues may be greater barriers to success in this endeavour than technical and scientific challenges. (Douglas 1996, p 185)

These factors operate at international, national and state levels in a complex interplay of funding and legal issues.

13.2 A HISTORY OF INTERNATIONAL IMMUNISATION PROGRAMS

13.2.1 THE EXPANDED PROGRAM ON IMMUNISATION (EPI)

At the international level the main players since the 1940's have been The World Health Organisation (WHO), and The United Nations Children's Fund (UNICEF). Initially WHO provided policy guidance on vaccine use for people of all ages, whereas UNICEF targeted paediatric vaccines. The Expanded Program on Immunisation (EPI) was established in 1974 and WHO provided administrative support while UNICEF was the main agency providing training, infrastructure support, vaccine supplies and equipment, for paediatric vaccines, to many of the world's developing nations. This program was effective in achieving its goals, and by the early 1990's the basic paediatric vaccines (polio, diphtheria, pertussis, tetanus, measles and tuberculosis) were administered to up to 80% of the world's children (IOM 1993).

The fundamental perspective from which these agencies work is underpinned by a model of medical science and economics that is predominately western, industrialised and reductionist (Kim et al 2000; Colgan 2002; Gillett 1994). The overwhelming majority of members of medical and technical advisory boards and organisational committees involved in the immunisation programs of WHO, UNICEF and EPI come from an educational and professional background that is recognised and accepted by the scientists and administrators of industrialised nations (WHO 1995; 2002a). In this capacity the WHO and UNICEF play an important trans-national role where parties with expertise from many nations work together to achieve a global goal.

It has only been at a local level, when dealing with issues related to accessing the population for immunisations, that some account may have been made for local cultural, religious and health traditions. The power and capacity for decision making at a national and trans-national level has been maintained by the industrialised nations, and those who support their perspective (Kim et al 2000, Colgan 2002).

13.2.2 THE CHILDREN'S VACCINE INITIATIVE (CVI)

By the late 1980's there was concern by those involved in the EPI about the increasing size of the project and the challenges of reaching the remaining 20% of the world's children in poor and remote areas. There was also a desire to develop new vaccines covering diarrhoea, malaria and respiratory diseases to add to the basic immunisation schedule. These factors led to the launch in 1990 of The Children's Vaccine Initiative (CVI) at the World Summit for Children in New York. This initiative formally named a wider range of supportive stakeholders. WHO and UNICEF remained the main players in the new program that now also included the United Nations Development Program (UNDP), the World Bank and the Rockefeller Foundation, with support from other agencies such as the US Federal Drug Administration (FDA), US Agency for International Development (USAID), US Centres for Disease Control (CDC) and various research institutes, drug manufacturers and donors (IOM 1993). As can be seen from this list, the new agencies formally involved in this coalition are predominantly from the USA. This drive for hegemony over immunisation by the USA is parallelled in the majority of areas relating to scientific research and medical health technology (Fischer 1990). Equivalent agencies and research facilities exist in many other developed nations, so the increasing involvement of the USA in international immunisation policy may have implications for future developments.

The CVI project was launched with the aim of increasing the immunisation rates of children in developing nations (Seattle P-I 2002a). They also proposed to "harness new technologies to advance the immunisation of children" (IOM 1993, p 2). At the summit

> It was proposed that the ideal CVI vaccine should be given as a single dose (preferably orally), effective when administered near birth, heat stable, contain multiple antigens, effective against diseases not currently targeted, and affordable. (IOM 1993, p 3)

Even in 1990 this was an ambitious goal, and the progress of research in the last ten years has highlighted how difficult, if not impossible, it would be to achieve. This is testified by Douglas of Merck Vaccines:

> The complexity of vaccine delivery today in clinical practice with 15-17 injections in the first two years of life emphasizes the need for development of combination pediatric vaccines, for example, putting DTaP, HBV, HIB and IPV together. This has proved to be far more difficult than previously believed due to unpredicted immune interference and incompatibilities on mixing of different components, demonstrating again the inadequacy of our understanding of how vaccines work and the empiric nature of the science. (1998, p 186)

The complexities of the task (see Chapters 4,5 & 6) are not the only factors, consideration also needs to be given to the strict guidelines and regulations that must be satisfied to obtain registration of a new vaccine, the high cost of research and development, the reduction in the number of drug companies able to sustain this type of research and the lack of profitable returns in supplying vaccines to developing countries (see Chapter 8).

By the mid 1990's several factors came into play that reduced the effectiveness of the CVI. Throughout the 1990's there were disputes between the WHO and UNICEF over the right of each organisation to formulate policy on vaccines. The AIDS pandemic and the push for an AIDS vaccine overshadowed the profile of

traditional paediatric diseases and vaccines. The rising cost and complexity of vaccine development, and the mergers and reductions in vaccine manufacturers, led to reduced interest in developing new, or improving existing, paediatric vaccines. There were also shortages in funding for the program (Seattle P-I 2002a).

13.2.3 THE GLOBAL ALLIANCE FOR VACCINES (GAVI)

In response to this situation, at the World Economic Forum in Switzerland in 2000, the Global Alliance for Vaccines (GAVI) was announced as another collaborative venture, initially for 5 years. It employs consultants and board members from a range of nations both developed and developing and has many of the same stakeholders as the CVI, including WHO, UNICEF, the World Bank, FDA, USAID, CDC, the Rockefeller Foundation and research and drug companies. This means that the majority of stakeholders, as with the CVI, are from the USA. The alliance is, however, steered by a significant new player also from the USA. The Bill and Melinda Gates Foundation initially donated $750 million dollars to launch the Alliance and have continued to contribute considerable financial support to a current total of $US 1 billion (Nossal 1999). In doing so they have positioned themselves as a major determining force in policy development and caused some controversy and raised substantial questions about valid goals and future directions. These issues will be discussed below.

The original players, WHO and UNICEF raised global immunisation levels from 5% to 80% between 1974 and 1990 (IOM 1993). Their major concerns by 1990 revolved around a lack of funding to develop new vaccines and distribute them to the remaining hard-to-access children. It is worth evaluating whether the formal involvement of an increasing number of agencies has actually supported the achievement of these goals. This is particularly the case as the largest new

agency, the Bill and Melinda Gates Foundation, has effectively transferred the locus of control from the offices of the WHO in Geneva to GAVI, based in Seattle USA. Three main issues need to be looked at here. Firstly whether the establishment of GAVI and consequent change in locus has facilitated the distribution of routine paediatric vaccines to a greater proportion of the world's children, secondly the current state of the vaccine manufacturing industry and thirdly the rationale underpinning the decision of the Gates Foundation to support immunisation.

13.3 GAVI AND THE CURRENT INTERNATIONAL SITUATION

13.3.1 EFFECTIVENESS OF GAVI

GAVI is promoted as a collaborative venture with all players given equal say and responsibility (Seattle P-I 2002a). However, this effectively demotes WHO and UNICEF who for the last 30 years have been the dominant forces in the field. When questioned about this by Paulson, a reporter for the Seattle Post-Intelligencer, Gates was evasive and effectively failed to answer this question:

> P-I: Once you decided to donate most of your foundation's resources to fixing problems in the global immunization network, why not just write checks and send them off to the United Nation's agencies, the World Health Organization and UNICEF, charged with this responsibility? Why create a whole new ballgame directed out of Seattle?
>
> Gates: Helping the World Health Organization and UNICEF is part of our agenda here. Nobody is trying to create an alternative. We just want them to do their jobs better, with more resources.
>
> P-I: Yes, but the Gates Foundation has significantly redefined how they will be doing these jobs and set up a new apparatus, the Global Alliance for Vaccines and Immunization, that effectively demotes WHO and UNICEF from their previous roles as decision makers for global immunization. Now they are marching to orders out of Seattle and are merely equal members with equal say in GAVI. Isn't that true?
>
> Gates: I'd want to be very careful about characterizing it that way. There have been scarce resources and we are providing more resources. It's a question about where you put them. . .
> (Seattle P-I 2002b)

The composition of the Alliance raises issues other than the apparent compromise of the traditional positions of both WHO and UNICEF. Concerns have been expressed that the governing board includes members of commercial vaccine manufacturers whose vaccines are promoted by GAVI. These include Aventis Pasteur that manufactures the DPTHepBHib vaccine, the Institut Pasteur of the yellow fever vaccine and the Centre for Genetic Engineering and Biotechnology of the Hib vaccine (SCUK 2002). Save the Children UK (SCUK) suggests that this apparent conflict of interest would be solved if a clearer distinction was made between the principles of partnership and governance.

GAVI policy places a priority on the inclusion of new combination vaccines in the immunisation schedules of countries for which it provides finance, despite the fact that there are areas that still lack the infrastructure necessary to provide the traditional vaccines. This is also despite the fact that The Technical Network for Logistics in Health (Technet), who have been advisors to both WHO and UNICEF since 1989, have advised that:

> Management and implementation of known technologies, rather than the development of new ones, must be the priority of health services logistics during the next 10 years. (Lloyd 1999)

Technet also emphasise the need to enhance transport, safe injection and disposal management systems, distribution and training, all of which are identified as areas where GAVI needs to substantially improve its performance (Lloyd 1999, SCUK 2002, Whitehead & Pasternak 2002).

The approach taken by GAVI has been called into question by its own board members, as well as by outside observers. Evans of the Rockefeller Foundation has called for clarification of GAVI's goals. Godal, the Executive Secretary of GAVI has admitted that it is still unclear how the various stakeholders and programs will

work together (Seattle P-I 2002c). SCUK has issued a detailed analysis of GAVI's performance based on studies done in developing countries that have been recipients of GAVI's support and have raised the following concerns and made the recommendations that are outlined in the table below.

An independent management evaluation by Mercer consultants also identified similar areas of concern including:

- time constraints.
- inaccurate demand forecasts.
- ineffectiveness of a loose alliance in implementing (vs developing) policy, with unclear and overlapping roles and a lack of accountability.
- discomfort with suppliers as partners in the effort.
- over emphasis on funding at the expense of advocacy and delivery.
- lack of clear management and accountability structure.
- inadequate assessment of issues relating to supply and individual nation program requirements.

(Whitehead & Pasternak 2002, pp 3 & 27)

RECOMMENDATIONS TO IMPROVE THE PERFORMANCE OF GAVI (from SCUK 2002)

No.	Concern	Recommendation
1	GAVI provides little funding for maintaining or strengthening immunisation provision systems such as training, waste disposal, staff salaries, transport and cold chain maintenance, without which sustained immunisation programs are not possible. Nations are paid an amount per child vaccinated, so this favours areas where the system support is already functioning and disadvantages those where the system is non-existent or experiencing considerable problems. Strengthening support systems is a long-term goal, and there are doubts that GAVI will survive long enough to genuinely address this issue.	That GAVI should substantially increase its level of support for systems costs and base its performance targets on system improvements.
2	The application process for GAVI assistance is complicated and time consuming and places disproportionate strain on nations with inadequate systems.	Recommendation: that GAVI should meet the costs of administration to fulfil their requirements.
3	Countries have felt compelled to make major decisions within very tight deadlines, eg when told its preferred DPTHepB vaccine was in short supply, Ghana was given only 10 days to decide on one of two alternatives, neither of which was suitable, and the resultant need to alter cold chain facilities led to a doubling of the cost of their immunisation program.	Recommendation: provide a suitable timeframe for countries to make significant decisions.

4	The introduction of new vaccines is being prioritised over the provision of the traditional ones. The routine EPI vaccines are only provided in combination with new vaccines such as HepB, Hib and yellow fever, yet there are still many nations experiencing difficulties in providing suitable coverage of the routine EPI vaccines, and adequate support should be provided in these areas before expensive new combination vaccines are introduced.	Provision of routine EPI vaccines should not be conditional upon introduction of new vaccines. Priority should be given to establishing effective immunisation systems where these are lacking. Countries should not be coerced into accepting combinations that they do not want.
5	The maintenance of cold chains is vitally important. Issues relating to provision and maintenance of fridges has not been adequately dealt with.	There needs to be priority given to the more expensive, but also more reliable solar fridges. Mechanisms need to be put in place to ensure their maintenance.
6	The new vaccines are supplied with single use, auto-destruct syringes, but this brings problems with waste disposal.	Effective waste disposal should be targeted as an area requiring training and ongoing support.
7	The tight time frame and considerable application process for GAVI meant that nations were unable to integrate this process with already existing immunisation programmes or to plan their application process through their Inter-agency Coordinating Committees.	GAVI needs to ensure that its application and reporting procedures integrate into those already existent in applying nations to avoid straining already fragile health administration systems.
8	Percentage of the population with immunisation coverage is the figure used to determine the type of support provided by GAVI. This data is unreliable and does not recognise significant variations between different areas within a nation.	GAVI either needs to support more accurate data collection, or consider alternative forms of application and performance requirements.
9	There are doubts that GAVI will exist for more than 5 years which makes it imperative that it contribute in ways that encourage the achievement of sustainable long-term improvements.	To achieve this it needs to prioritise the development of sustainable support systems in ways that reach areas that are currently struggling to provide the routine EPI vaccines.

From these detailed and independent studies it would appear that GAVI has introduced new complexities into the old system of distribution. GAVI has used inadequate data collection methods to evaluate vaccine needs, instituted complex application procedures that have strained the resources of developing nations and insisted on the introduction of new combination vaccines that have not always been suitable for the needs of the target population. In order for GAVI to ensure that it is reaching those children most in need,

> . . . it should consider how to ensure it does not simply support areas with functioning or near-functioning immunisation systems, but also targets those areas where these systems have ceased to function. (SCUK 2002 p Ia)

Given that the main concern before its establishment was to facilitate distribution of the traditional vaccines to the 20% of the world's children who did not have access to them, it would appear that GAVI's mode of operation has not facilitated this process.

To examine some of the reasons why this situation has arisen it is useful to examine aspects of the rationale behind the establishment of GAVI and the decision of Gates to become involved in international immunisation programs. This will be examined in Sections 13.3 and 13.6.

13.3.2 BILL GATES AND GAVI

When asked why he was concentrating on immunisation rather than on programs designed to alleviate poverty Gates replied that:

> Poverty and disease are connected, no question. But I don't think it's correct to say poverty causes disease. It's more the other way around. People – economists and other experts on all this – are beginning to recognize that. (Seattle P-I 2002b)

This view is also endorsed by Godal, Executive Secretary of GAVI who states that:

> . . . diseases and their underlying causes can affect the economies of families in a number of ways: Reduced productivity, impediment of education or retained high dependency ratios. The emerging conclusion is that the right investment in health is at least as important as education. (Godal 2000, p 160)

Whilst one would not dispute a statement couched in these terms, the implication is once again that the causation is simple and lies in one direction, ie, that poor health is causing poverty. The situation is not that simple, nor is the causation, as the following discussion demonstrates.

As demonstrated in Chapters 11 and 12, there is a growing body of evidence to suggest that a considerable proportion of the causation is in fact the other way around and that poverty is causing disease. Many other factors, most importantly economic and environmental ones, impact on the health of nations and individuals. Western thought, and particularly western medicine is characterised by a reductionist perspective and a penchant for easy, quick-fix solutions (McKeown 1979; Gillett 1994). Population health issues do not sit easily within this framework because they are intrinsically complex.

The most significant differences in perspectives on health underpinned by a neoclassical economic perspective, compared with those arising from public or community health approaches can be characterised as follows. The neoclassical economic approach as espoused by the World Bank, the International Monetary Fund, and now Gates and others through GAVI, is based on the notion that a population is comprised of individual economic actors. Healthy individuals are more economically active and therefore more viable. The charity dollar and governing style are aimed at directly improving the health of individuals to increase their economic viability and therefore the economic viability of the nation as a whole (Kim et al 2000; McKeown 1979).

In contrast, the public or community health approach sees the members of a population as interconnected. Poverty and ill health are not just a result of individual mischance, they are influenced both positively and negatively by the structural function and power distribution of the community as a whole. As such, the influence of government policy in all areas of governance is considered relevant to the health and welfare of the population (McKeown 1979).

> Public health refers to those efforts that are organised by society, through governments, to protect, promote and restore the health of a population. The emphasis is placed on a totality of endeavours . . . (Palmer & Short 1994, p 53).

The evidence presented in Chapters 11 & 12 supports the public health perspective. It counters the assumption made by Gates and other proponents of neoclassical economics that improving the health of individual members of society, and presumably thereby increasing their potential for productivity (Godal 2000) will solve the complex social and economic problems of developing nations. These problems include the growing inequities in wealth and access to resources that are underpinned and exacerbated by the loan repayment requirements and structural adjustment programs imposed by the World Bank and the International Monetary Fund (Kim et al 2000). These policies, based on neoclassical economics, have emphasised privatisation of government facilities and user pays schemes, both of which have been shown to deter access to health services by the poorer members of society (England et al 2001). The growing inequity in wealth, both on a national and international level, that has resulted from these policies has been a fundamental cause of poor health in both developing nations and lower socio-economic groups in industrialised nations, as demonstrated in the following quote:

> Important for health, above all else, is a basic level of wealth sufficient to supply essential needs such as food, shelter, clothing and warmth. . . Inequalities in wealth and power lead to inequalities in health by determining the social circumstances in which people work and live. . . Economic inequality may affect health both directly and indirectly through psychological and social processes, by effects on self-esteem, and on social relations generally. . . Poor people have less to spend on nutritious food, clean water, adequate clothing and shelter, all of which are essential to a minimum level of health and well-being. They have less access to education and political power that is needed to improve and safeguard health. . . . An important first step is recognition of the need, in the interests of health, for income redistribution policies. Economic growth alone is insufficient to overcome absolute poverty and will have little impact on relative poverty. (Beaglehole & Bonita 1997, pp 46-50)

Alleviating poverty, ensuring adequate nutrition, access to clean water and family planning services are important preventative health measures, so also is a sense of support and involvement from both the government and local community. These factors have been shown to have profound effects upon general health and life

expectancy that outweigh the provision of specific health measures such as immunisation (see Chapters 11 & 12; Caldwell 1986; Evans Barer & Marmor 1994; Kim et al 2000; Seattle P-I 2002d; Woodward 1992).

However, addressing issues such as these raises more complex social and economic issues on both a national and international level. It brings into question the relationship between developed and developing nations and the roles and priorities of agencies such as the World Bank, the International Monetary Fund, USAID, and transnational corporations such as the drug companies which produce the vaccines.

> The spending of billions of dollars on [vaccine research] has to be seen against an economic background in which the simple dependency of Western capitalism on Third World labour and resources is undergoing a complex set of transitions which include an increased exploitation of the Third World through aid and development, and the piracy of Third World intellectual and biological resources. These processes intersect with transitions in science itself. Science is becoming bigger and more capital intensive, more commercialised and more directly connected to private capital. This transition is particularly marked in biomedicine, which has always been an inherently applied and commercial science, resulting in corruption at one extreme and a shift in the nature and ownership of intellectual property at the other. (Turnbull 2000, pp 166-67)

It also brings into question the rationale behind the decision of trust funds such as the new Bill and Melinda Gates Foundation to support immunisation over the many other health improvement approaches available, and their attempt to justify this on a simple “health equals wealth” aphorism. This will be addressed in more detail in Sections 13.5 &13.6.

13.4 THE CURRENT STATE OF THE VACCINE MANUFACTURING INDUSTRY

There are several trends evident in the development of the vaccine manufacturing industry that will be discussed in this section:

- Vaccine manufacturing companies in industrialised nations, which are also involved in research, are tending to merge into large multi-national corporations.
- Developing nations are building their own manufacturing plants, at least for the easier to produce traditional vaccines.
- There is an emphasis on producing combination vaccines that are technically more complex and more expensive to produce than the traditional ones. This carries with it the need to recoup investment costs.
- There is a trend to conduct efficacy studies in developing countries to reduce costs. This has both scientific and ethical implications.
- The need for manufacturing companies to adhere to government legislation as well as maintain profitability tends to give rise to ethical conflicts in their role as providers of a preventative health measure for healthy children.

13.4.1 MERGERS

Between 1966 and 1977, half of all US commercial vaccine manufacturers stopped producing and distributing vaccines. Between 1985 and 1995 the number of producers reduced from seven to four, with only two actively developing new vaccines. Since then there have been further mergers and now only Merck & Company Incorporated and Wyeth Lederle Vaccines & Pediatrics remain US owned (Mowery & Mitchell 1995; WHO 2002b). The trend has been similar in other industrialised nations, for example the recent merger between Glaxo and SmithKlineBeecham into GlaxoSmithKline. The history of takeovers and mergers in the past decade is extremely complex with a distinct trend towards increasingly large multi-national corporations (Mowery & Mitchell 1995).

Although the drive to increase market share and profitability is undoubtedly the main motivating force amongst these large corporations, the increasing costs of research and development, and the need to share patents and resources are also significant factors behind the mergers of vaccine producers. Before the mid-1980's there were very few patents. For example, in the USA in 1983 there were two patents for 27 vaccines, but in 1993 SmithKline Beecham had to assemble 14 patents just to produce and market Enerix B, their Hepatitis B vaccine. This situation has led to a proliferation of co-development and cross licensing

agreements amongst firms from different nations, as well as to increases in production costs (Mowery & Mitchell 1995).

The reduction in number of manufacturing firms and the high degree of specialisation that arises from the development of technologically complex vaccines has resulted in vulnerability of supply. A few nations such as Cuba, India, Korea, and Senegal have built their own manufacturing plants for one or more of the traditional vaccines, and WHO is able to source most of these traditional vaccines from more than one country for supply to nations in need, although they do not test or control for quality (Mowery & Mitchell 1995; WHO 2002b). However, as discussed in Chapter 10, many of the more technologically complex combination or specialty vaccines are manufactured by only one plant. Industrialised nations who use these routinely, and the developing nations who are being encouraged to use them by GAVI, are therefore vulnerable to interruptions in supply. This situation occurred recently in the USA when they experienced shortages of several vaccines including DTaP, MMR and pneumococcal conjugate as a result of manufacturers ceasing production, changing production methods, demand exceeding production, regulation compliance and distribution issues (NNII 2002). Interruptions to supply can occur for many other reasons including accidents, equipment or batch failure, industrial action or terrorist attack. The effects of an incomplete series of vaccinations, or of having to change vaccine during a series is a complex issue owing to the number of different combination vaccine options available and the tendency for some vaccines to react with or interfere with the actions of others. This has not been fully researched (Blackwelder 1995; Brahma Reddy 1987; Daum, Jain & Goldstein 1995; Fine 1997; Miller 1999; Mowery & Mitchell 1995).

13.4.2 CONSEQUENCES OF NEW TECHNOLOGIES

The last decade has seen the development of several new vaccines, particularly combination vaccines, in response to the perceived need to reduce the number of injections in the current paediatric vaccine schedule. Even in relatively well organised industrialised nations the availability of a range of combination vaccines has increased the costs of administration and the complexity of record keeping (Daum, Jain & Goldstein 1995; Mowery & Mitchell 1995). The introduction of these vaccines into the schedule recommended by GAVI has brought challenges to the developing nations who have qualified for assistance. These challenges have included decisions about which combination vaccine to introduce, needs to alter cold-chain facilities to cope with the new requirements, difficulties with record keeping, problems with training health care providers and accessing populations in remote areas. None of these issues are taken into account during the trials of vaccine efficacy, the results of which are used to market the vaccines to these countries (Clemens et al 1996). This situation was exacerbated by the trouble GAVI had ensuring supply of promised vaccines. Some nations, such as Ghana, Mozambique and Tanzania faced problems when their preferred DTPHepB vaccine was in short supply and they were given little time to consider alternative options (SCUK 2002, p 1c).

The high degree of reliance of developing nations on subsidised vaccine supplies means they are likely to be more vulnerable to alterations in the availability of combination vaccines and the consequent problems with interrupted and altered courses of vaccines. The introduction of combination vaccines into the schedules of developing nations has also increased vulnerability of supply because it has increased the cost of supply. With the traditional vaccines of the past, children in both industrialised and developing nations received the same vaccines. The industrialised nations paid higher prices for the vaccines, thus subsidising their supply to developing nations. All six traditional vaccines could be supplied to a child

in a developing nation for about US$1. In 1986 the new HepB vaccine was marketed at US$150 for a three dose schedule. This led even a relatively affluent industrialised nation like New Zealand to examine ways to cut costs by reducing the dose. They found a found a substantially reduced dose to be highly efficacious, which raised issues for neonatal tolerance and dose determination research and their relationship with industrial issues such as sales and profits (Goldwater 1993).

The previous tiered pricing arrangement suited both parties:

> . . . UNICEF secures cheap vaccines while manufacturers profit from a guaranteed market of millions of doses of vaccine – albeit at lower prices – and gain a potential foothold in other developing country markets. (WHO 2002c)

However now, given the high cost of vaccine development, there is little likelihood of vaccine manufacturers offering new products at reduced prices. The serious implications of these changes in the industries are outlined in detail in this quote from a recent media release from UNICEF:

> With industrialized countries now buying new vaccines, the low prices at which UNICEF had been able to buy traditional vaccines were threatened.
>
> Vaccine manufacturers began phasing out the production of the traditional, less expensive vaccines used in developing countries. Between 1998 and 2001, 10 of 14 manufacturers partially or totally stopped production of the traditional vaccines. Eight of these firms were the main suppliers of vaccines to UNICEF. Six of the eight were involved in mergers between larger pharmaceutical companies. . .
>
> The overall outcome is that the availability of vaccines to UNICEF has dramatically decreased. . .
>
> Vaccine prices have also increased. Between 2000 and 2001, for example, the cost of vaccines for DTP rose by 15 percent, measles by 10 per cent, and TT by 23 percent; the prices are likely to climb even higher. . .
>
> The combination of reduced availability of vaccines and fewer manufacturers creates a high risk to vaccine security . . . This narrowing between availability and demand means there is no allowance or safety net for variations in vaccine yields, batch failures and slow regulatory release. (WHO 2002c)

This statement is contrasted with the fact that the global market for vaccines has grown at an annual rate of 10% since 1992, from $2.9 billion to $6 billion US dollars. The growth is forecast to continue, but has arisen from an increase in vaccine prices of an average 6% per dose annually, and the demand in industrialised nations for higher priced vaccines, not from an increase in volume of sales.

> High-income country demand represents 82% of industry revenue, but only 12% of volume. Increasingly, high-income country immunization schedules are diverging from those in low and middle countries. (Whitehead & Pasternak 2002, p 1)

As a result of these market changes, the profitability of the transnational producers is considered higher now than it was ten years ago, and company figures show anticipation of a continual increase in returns on investments (Whitehead & Pasternak 2002).

There is a difference in market strategy between transnationals based in the USA and those based in Europe. U.S transnational companies concentrate their business, research and development on a small number of proprietary products with high profit margins, and drop “mature” products from their portfolios when they are deemed no longer sufficiently profitable. European transnationals concentrate on building “suites” of products with both monovalent and combination vaccines, enabling them to serve a wide range of buyers and markets. The US transnationals are higher-cost producers than the European transnationals, because their volume of production is significantly lower. Therefore the European transnationals are in a better position to maintain their involvement in international immunisation programs. Newer suppliers in other nations have less capacity for research and development, and so they tend to focus on providing low cost supplies of basic paediatric vaccines to low and middle-income nations through agencies such as

PAHO, UNICEF and GAVI (Whitehead & Pasternak 2002 p 18). Their continued involvement in international immunisation programs is therefore most secure.

All three types of suppliers are engaged in and committed to low-income nation immunisation, but there are three main pressures on this commitment. They are:

- Absolute capacity constraints.
  Prior to the 1990's capacity limits were not an issue, but now that transnational suppliers, from both the US and Europe, have specialised and rationalised their bulk production and filling operations there has been a significant reduction in production relative to demand. Also, the demand from high-income nations for single dose packaging has placed pressure on the filling capacity of these companies.

- Opportunity costs.
  New opportunity costs have put international agencies in competition with other bulk markets, and the specialisation of production plants has exacerbated this. For example:

  > The diphtheria toxoid component of [GlaxoSmithKline's] DTP-HepB combinations for GAVI is also used in its DTaP and DTaP combinations sold to high income country buyers; the tetanus toxoid component is used not only for these other products but also as a carrier protein for its Hib products. Faced with capacity constraints, suppliers are likely to allocate antigens based on the absolute and relative profitability of buyers and products. (Whitehead & Pasternak 2002, p 21)

- Regulatory pressures.
  There is an increasing divergence between the regulations and vaccination schedules of high-income and low-income nations.

  (from Whitehead & Pasternak 2002, pp 21-23).

These pressures have a greater effect upon the transnational companies than upon the newer companies who are more oriented to production for bulk supply to low and middle-income nations. It is ironic that it is the USA that is the dominant force in the policy and administration of international immunisation programs, when it is the USA based transnational companies whose involvement in this market is most fragile.

13.4.3 EFFICACY TRIALS AND ETHICAL ISSUES

To reduce the considerable costs of research and development, there is an increasing trend to conduct Phase II and III studies in developing nations. This is primarily because wage costs can be less than 10% of those in industrialised nations (Whitehead & Pasternak 2002). Phase III trials, which need to cover anything from hundreds to tens of thousands of participants are now particularly likely to be conducted in developing nations. The easiest, and cheapest way to gain regulatory approval of a new vaccine in the USA is often to conduct a large efficacy study in an appropriate foreign population, and then a small "bridging" study to confirm the results in the corresponding US population. This strategy must be highly cost effective as it is frequently pursued, despite

> . . . the potential regulatory problems that can occur when vaccine efficacy trials are not conducted in the target population for which approval is sought. (Davenport 1995, p 87)

.

However this strategy raises significant ethical problems that have been raised in relation to other medical treatments and drugs such as AZT and AIDS vaccines. These issues include the exploitation of vulnerable populations, the influence of corruption on results obtained and racial and ethnic variations in immune response that complicate the extrapolation of results from one racial or ethnic group to another (Davenport 1995; Hellman 1998; Kim et al 2000; Luna 1999).

13.4.3.1 Exploitation and Corruption

Nations vary considerably in their degree of structural, or entrenched, corruption. From studies done by Transparency International, some nations, such as Finland and Denmark are seen as having very low levels of corruption, whilst others, such as Argentina, Russia, Uganda and Colombia are seen as having very high levels of corruption (Transparency International 2003). In impoverished nations, research and incentive practices that are considered acceptable in more affluent nations may exert a disproportionate influence. In nations where researchers and

physicians in public institutions have comparatively low wages, industry provision of dinners, travel to conferences, payment per research subject involved in a study or supplies of equipment may act as considerable incentives. The researchers may feel obliged to provide the industry with the results it desires to ensure continued association.

> [In Argentina] it is informally known that in many cases 'industry' pays extra money to researchers and physicians working in research: they even pay per each research subject enrolled in a study (which may raise doubts as to the adequate selection of certain research subjects). Notice that in these cases, money is not delivered to the institution nor does it have a transparent way of being allocated; it goes directly to the pockets of the researchers who, as I said, are not well paid. (Luna 1999, p 267)

As most research is conducted through public institutions, it is generally the poorer and therefore more vulnerable members of society that are likely to become involved in these research studies. In these nations it may be easier to encourage research participants by offering measures such as free vaccinations or other complimentary health services, that would not necessarily be seen as sufficient incentive in more affluent nations. These people may also be illiterate and thus unable to fully understand any educational information provided, or lacking in awareness of their rights as participants, despite genuine attempts to obtain informed consent (Luna 1999).

Another factor to be considered with research conducted in developing nations is that mechanisms of control over research may be lacking. Requirements for approving research may be easier to meet, ethics committees may be inadequately educated or under pressure to approve the research, there may be fewer regulations on patents (Luna 1999).

The majority of vaccine efficacy studies are conducted by only the largest transnational corporations who are increasingly conducting research in developing

nations. This is not to say that these companies intentionally indulge in corrupt practices, nor is it to say that results of efficacy studies have been influenced by corruption. However, the possibility for this to happen definitely exists, and should be acknowledged.

> A first step in preventing possible corruption consists in the obvious fact of recognizing its possibility and its pervasive effect even in research. It is essential to be aware of the different rules (formal and informal) that might be present in the various countries with different traditions. (Luna 1999, p 268)

Practices that raise ethical considerations are not confined to developing nations. In 2001, the USA transnational drug companies spent about $78 million US on political lobbying and employed over 600 lobbyists. This is more than one lobbyist for each member of congress. GlaxoSmithKline, a significant developer of paediatric vaccines increased its lobbying expenditure by 28% from 2000 to 2001 (Public Citizen 2002).

The legislation the drug companies lobbied on in 2001 included paediatric issues. Specifically, legislation was re-authorised granting companies an extra six months of patent monopoly if they tested the safety of their drugs in children before releasing them for paediatric use. Also, various legislations were passed protecting the interests of private health insurers. This directly impacts on immunisation in the USA, as more affluent members of the community with private health insurance are more likely to use the more expensive combination vaccines than are poorer people who rely on basic government subsidised vaccines (Katz 2001; Sardell 1990).

Although new drugs and vaccines must be passed by the FDA before public release, there is evidence that large corporations who have invested heavily in the

development of a new products place considerable pressure on the committees to have their product approved.

> FDA Medical Officer Robert Misbin, the scientist who blew the whistle on the dangers of the diabetes drug Rezulin, resigned Monday, complaining that politics and bureaucratic concerns are replacing sound medical judgement in approving drugs . . . (CBS News 2002, p 1)

In 1999 a new rotavirus vaccine was withdrawn from the market after less than a year for causing bowel obstructions in babies.

> The CDC [Centre for Disease Control] had voted to recommend that all babies get rotavirus vaccine weeks before the FDA Committee voted on scientific proof of safety and efficacy. (Fisher 2002, p 4)

Similarly the CDC's Policy Committee voted to recommend "universal use" of Prevnar vaccine before the FDA Committee had reviewed the data or voted on whether it should be licensed (Fisher 2002). Also, before the FDA had approved licensure, the developing company and Kaiser Permanente, a health insurance company (Kaiser Permanente 2003), were promoting it as a vaccine against ear infections, when the company's data showed it only decreased the chances of ear infection by 7%. Prevnar vaccine was the best selling new pharmaceutical in 2000 with sales of over $450 million US.

> The FDA has never licensed Prevnar as an ear infection vaccine but lots of doctors in America tell parents it is because that is how the vaccine has been promoted. (Fisher 2002, p 4)

Fisher, the consumer member of an FDA Committee was the only committee member to vote against the approval of the Prevnar vaccine because of methodological flaws in the safety trials. These cases demonstrate that there are problems with policy formulation, protocol and vested interests of committee members. This is reinforced by the following comments from people who have

served on the United States Advisory Committee on Immunization Practices (ACIP):

> I've sat through their meetings and know pretty much what goes on there. Basically they rubber-stamp whatever the drug companies put in front of them. But this committee comes up with language saying, such and such a person should get this vaccine at such and such a date. Then the drug company lobbyists take that recommendation from the ACIP and they go around to all the state legislatures and state health departments saying "Did you see what the CDC [Centre for Disease Control] says to do?" And the American Academy of Pediatrics, of course, jumps in. There are huge donations flowing back and forth between all these people. It's a huge conflict of interest. (Belkin 2002, p 1)

> ACIP, a small group whose members have incestuous ties with agencies that stand to gain power, or manufacturers that stand to gain enormous profits, from the policy that is made. Even if such members excuse themselves from specific votes, they are permitted to participate in discussions and thus influence the decision. (Orient 2002, p 1)

The FDA has been criticised by the United States Government Accounting Office, an investigative department of Congress:

> Federal control of new drug testing is not adequately protecting human test subjects and the public. (GAO in Brandt 1979, p 589)

Other investigators have also made similar claims:

> . . . the FDA has approved new drugs for public use on the basis of highly questionable data. FDA attempts at self-investigation have proven largely useless. (Greenberg in Brandt 1979, p 589)

> The FDA has failed to enforce its standards and, according to many reports, has served as a lackey to the major pharmaceutical companies. (Mintz in Brandt, p 589)

> In its mission of public protection, the FDA, by any standards, has proven to be grossly inefficient. (Brandt 1979, p 589)

The issues that have been raised here in relation to corporate policy and influence are common to many areas of medicine where companies have invested large amounts of money into the development of technology and drugs (Charlesworth et al 1989; Harvey & Murray 1995; Mann 1976; Richards 1991).

A significant difference between immunisation and other medical treatments is that immunisation is a preventative health measure. It is administered to what the literature refers to as healthy children, and is legislated as compulsory in most states in the USA, with medical and conscientious objections difficult to obtain. Under these conditions the government has a responsibility to ensure that the vaccines it licenses should be as safe as possible (Dare 1998; Goodman & Goodman 1986; Pellegrino 1984). However, the government of the USA is protected by "sovereign immunity". This means that the government, or sovereign, "cannot be sued for negligence without its consent" (Akula 2000). Akula notes that:

> The fact that Americans have little trust in government, especially when it comes to health care, is often noted but little understood. The distinctive [and lower] legal standards that apply to government's accountability provide insight into this mistrust. . . these legal standards may also prove a serious obstacle to government's successfully carrying the responsibilities of a broader role in the health care system. (2000, p 152)

When the FDA and National Institutes of Health (NIH) have been challenged for their roles in the licensing and release of vaccines,

> . . . the courts have outlined the appropriate analysis: It must be determined whether an agency goes through each step specified in the applicable rules, because as to required steps there is no discretion and no immunity. However, whether these rules are sound is beyond legal challenge, and so is the soundness of any judgement calls permitted by the rules or absence of rules . . . The negative stereotype of the "bureaucrat", proceeding down a rigid checklist and otherwise indifferent to the soundness of his or her actions, is a good fit with this legal standard, although this approach in the private sector would invite liability.(Akula 2000, p 155)

This is why it is possible for the FDA to recommend universal administration of a vaccine when there is insufficient evidence of its safety. As long as the protocols are carefully followed there is no liability on the decisions (see discussion of Prevnar vaccine above and Fisher 2002). Given the above evidence, it would appear that the responsibility of the government to ensure the safety of vaccines has, in some cases, been compromised.

13.4.3.2 National variations in immunisation provision

There are considerable variations in national practices and abilities to provide health care in general, and immunisation in particular. These also impact upon the validity of efficacy studies (Clemens et al 1996; Streefland, Chowdhury & Ramos-Jimemez 1999). A comparative study conducted in five nations (Bangladesh, Ethiopia, India, Malawi and the Phillipines) identified a range of problems with immunisation delivery that ranged from physical accessibility to social custom.

- There was considerable variation in times when immunisation was available. These ranged from 4 days a week at a fixed location, to monthly at outreach centres. All nations experienced abrupt stoppages or cancellations of sessions, which were problematic for mothers who had to travel considerable distances. National immunisation days interrupted normal availability by up to three months in isolated areas.
- Sometimes there were considerable waiting times. In India all children from higher castes had their immunisations first, and children from lower castes had to wait until all the higher caste children were completed, even if they arrived late.
- All nations experienced shortages in supplies of vaccines, record cards, stationary, needles and syringes. Researches observed the use of needles still hot from sterilisation, multiple use of the same needle, and use of blunt needles.
- There was a considerable range of skill in health workers. Some were obviously untrained and injection sites bled or became abscessed and infected. Some injected just under the skin, others injected deeply. Depth of injection is important for the success of the immunisation (see Diggle & Deeks 2000; Zuckerman 2000)
- Educational information was not always available, and varied in quantity and quality. Some health workers conveyed misinformation.
- In all nations there were notable reports of health workers being impolite and sometimes rude to mothers. For example shouting at them for being late, or stopping work at midday even when mothers were still waiting who had travelled considerable distances. In India some health workers refused to immunise children of mothers who were not using birth control.
- All nations had inadequate systems for registering immunised children and very little capacity to follow up on parents who were non-acceptors or who failed to complete a series.

(Streefland, Chowdhury & Ramos-Jimemez 1999)

To be fair, many of these problems also exist to some extent in industrialised nations including the USA and Australia (Herceg, Johns & Longbottom 1997; Murphy, Pastor & Medley 1997). The five nations surveyed in this research had relatively well developed immunisation systems, there are many developing nations where the problems of funding, supply and access are more severe. Experimental

vaccines may be administered at normal immunisation visits (see for example Åhman et al 1999; Eskola et al 2001) both to reduce costs and for ease of access to the target population. The trial vaccines are also

> . . . formulated with the goal of maximizing immunogenicity, not with the goals of increasing convenience and practicality . . . efficacy trials usually focus only on adverse effects that are expected on the basis of earlier studies, that occur shortly after vaccination and are frequent, and that are easily measured with symptom questionnaires and other available instruments . . . efficacy trials are primarily driven by a focus on evaluating vaccine protection. (Clemens et al 1996)

which means that minimal consideration is given to field conditions, and efficacy trial reports are notoriously lacking in information regarding organisational details and problems and issues encountered in conducting the studies (Chalmers & Altman 1999; Clemens et al 1996; Hellman 1998).

The use of developing nations for efficacy trials means that they are likely to be conducted in sub-optimal conditions, with problems of administration in both the delivery and record-keeping senses of the word. The use of a small bridging study to confirm results for a population in an industrialised nation may not be sufficient to reveal inadequacies in the data of the larger studies.

13.4.3.3 Variations in population immune response

As discussed in Sections 2.7 and 8.4, there are considerable variations in the characteristic immune responses of different ethnic and racial groups (Hsu 1996; Poirer, Poland & Jacobson 1996 ; Worku 1997). On an immunological level this creates difficulties in extrapolating results from one ethnic or racial group and another, even within the same nation. There may also be characteristic disease profiles that influence the efficacy of vaccines, as well as characteristic strains of pathogens in different geographical areas (Broome 1991). For example the vaccine against tuberculosis that is effective in Britain does not work in Africa because of the presence of local mycobacteria (Turnbull 2000, p 169). Also, in areas where

poliovirus is endemic it important to give OPV concurrently with an injected vaccine, particularly DTP or related trial vaccines. This is because intramuscular injections can trigger paralysis in infected individuals thus affecting immunisation outcomes (Muragasampillay 1994).

> Even among ideally designed efficacy trials, differences in genetic and other host characteristics, in qualitative features of antigens of target pathogens, and in the incidence and seasonality of infections may produce trial-to-trial differences in vaccine protection. Moreover, to the extent that efficacy trials depart from the ideal paradigm by, for example, enrolling individuals who are not completely healthy or who manifest some degree of natural immunity, intertrial differences in these features may yield disparities in vaccine performance. (Clemens 1996, p 392)

The systemic population health issues raised in Chapters 11 & 12 exacerbate this situation, as broader health factors such as poverty, malnutrition, nutritional deficiencies, chronic infections and stress all influence the capacity of individuals to mount appropriate immune responses to vaccines. Therefore trialling a vaccine in a population in a developing country where one or more of these factors is present may significantly alter study results. The practice of using the populations of developing nations to trial new vaccines and other drugs is considered by some researchers to be a medical equivalent of the colonisation of developing nations and the utilisation of their economies to "facilitate capital accumulation and consolidation (Whiteis 1998) (see for example Bland 1994; Merson 2000; Nations & Monte 1996; Schiele 1996).

The same considerations come into play if a vaccine is trialled in a poorer cohort in an industrialised nation. Here the relationships between the wealthy and "impoverished local sectors mirror similar relationships between First and Third World countries" (Whiteis 1998).

13.4.3.4 Implications for efficacy trials.

In conclusion, the trend for the few transnational corporations still involved in research and development of vaccines to conduct efficacy trials in developing nations raises significant practical and ethical issues. Reward and payment schemes that are standard in affluent nations may act disproportionately as incentives to researchers to provide what are perceived as desired results. Research controls may be inadequate, or there may be perceived pressure to approve study protocols. Study populations may be vulnerable to incentives, or inadequately informed. Results obtained from studies in these populations may have limited extrapolation value due to broader genetic and health issues.

In industrialised nations, the policies and protocols set in place to control licensure of vaccines and ensure their safety, may be overridden by the power and influence of the manufacturing companies. Politicians who formulate these policies and protocols may be subject to intense lobbying by representatives of these companies who are employed with the explicit intention of preserving their interests.

13.5 OTHER IMPORTANT PUBLIC HEALTH ISSUES

Some consideration needs to be given to the question of why the Gates Foundation has decided to put funding and influence behind immunisation, rather than any other aspect of public health.

It is estimated that at least 20% of the world's population do not have access to safe drinking water. More than two million people a year die from the large number of water borne diseases including diarrhoea, enteric diseases, parasites and infections for which there are no available vaccines, and many more become seriously and/or chronically ill. In addition to this it has been estimated that over 10 million person-years of effort are expended annually by women and female children

carrying water from distant sources (ESW 2002). Apparently, the major resources needed here are not primarily funding but organisational, in terms of meeting community needs, adhering to project design standards and service maintenance (ESW 2002). As such they reflect many of the same requirements as a successful immunisation program.

However, they differ in that they need to be designed to meet the needs of the specific target community, and more significantly, they need to be designed in such a way that the facilities can be simply maintained on a long-term basis by that community. To be genuinely successful, they offer limited scope for the ongoing involvement of transnational corporations and industrialised nations, and therefore limited scope for profit. The World Bank and IMF have insisted on the privatisation of services such as water provision in their Structural Adjustment Plans (SAPs). In areas where the provision of water has been privatised, including in the USA, the projects have been generally been unsuccessful (Akande 2002; ESW 2002; Millen & Holtz 2000).

The provision of a regular clean water supply is an essential aspect of public health that is most effectively addressed in an holistic community-appropriate approach, that reaches all members of a community, rather than one open to privatisation and motivation for profit. There is also the consideration that vaccinating a young child will not be optimally effective if they are still at considerable health risk of infectious disease from unsafe or inadequate water supplies.

Adequate nutrition is another fundamental requirement of health. It is well known that even minimal deficiencies in vitamins and minerals can have significant detrimental effects upon the health of both individuals and population groups, and that the risk of such deficiencies varies with physical location, dietary patterns and

genetics (See for example Chandra 1981; Hussey & Clements 1996; Kalokerinos 1974; Nieman 1999). It is also well accepted that certain essential nutrients are of fundamental importance for the effective functioning of the immune system, and that individuals who are deficient in these nutrients are not only at greater risk of infection, but also lack the ability to mount an appropriate response to an administered vaccine.

> Grossly inadequate intakes of protein and other specific nutrients are today resulting in extreme degrees of malnutrition and concomitant infectious disease. It seems likely that the interactions between nutrition and infection are more important in animal and human populations than one would predict from the results of laboratory investigations. It must be remembered that the interaction between nutrition and infection is dynamic, being frequently characterised by synergism and less commonly by antagonism, and that control of malnutrition and infection are interdependent, so that the course of a disease is intimately related to the nutritional status of the host. (Newberne & Williams 1970, p 93)

This is the reason why Vitamin A is frequently administered with measles vaccine, particularly in developing nations in Africa where the population is known to be prone to Vitamin A deficiency (Hussey & Clements 1996), and why Dettman (1972), Kalokerinos (1974) and others so strongly advocate Vitamin C supplements with immunisation for Australian Aboriginal populations.

> . . . it has been shown that infants suffering from protein-calorie malnutrition may exhibit a 'reversed immunological effect' when immunised. Usually, an immunisation results in a rise in antibody levels (that is how they work). However, in protein-calorie malnutrition levels may fall; an infant is thus exposed to all sorts of serious infections and possible death. (Kalokerinos 1974, p 83)

There is therefore little point in administering vaccines to individuals whose nutritional status is compromised so that they are unable to mount an appropriate response to an administered vaccine. It is also not sufficient to administer vaccines to populations who lack access to an adequate supply of clean water, as both

adults and children are still at risk of contracting any of the vast number of debilitating and chronic diseases for which there are no vaccines.

Another aspect of public health that may have significant benefits for the health of both women and children is the provision of family planning facilities as part of a comprehensive public health approach. The current situation with regards to international family planning services provides an example of the way that political agendas can influence the provision of health services. The Republican government of the USA under George Bush has recently stopped grants to the United Nations Family Planning Service and International Planned Parenting Services as a result of pressure from strong anti-abortion lobby groups that exist in the US. Under the Clinton administration, the USA had donated as much as US$35 million to these services (IPPS 2003).

As can be seen from these examples, it is inadequate to offer increased immunisation coverage if the health of all members of the community is being jeopardised by lack of access to basic public health facilities such as clean water, adequate nutrition and family planning where desired. This is true of all populations, whether in industrialised or developing nations.

Immunisation deserves to be regarded as a useful component of public health care, but cannot be considered a primary factor to be administered in isolation from a comprehensive public health plan. On its own it is not a sufficient measure to improve the general health of a population, nor alleviate poverty. It is therefore worth postulating some of the reasons why so much emphasis is placed on immunisation, and why it has attracted the involvement of someone like Gates, these will be addressed in Sections 13.6.2 & 13.6.3.

13.6 IMMUNISATION AS AN INTERNATIONAL PUBLIC HEALTH MEASURE

A question that remained unanswered in Section 13.3.1 was: 'Why would the United Nations agencies WHO and UNICEF agree to enter into a partnership such as GAVI?' Previously they were the main agencies in control of global immunisation policy and distribution. Now they are in equal partnership with many other organizations and the locus of control has shifted from their home in Geneva to Seattle, USA, with the Bill and Melinda Gates Foundation. Gates offered no clear explanation as to why the organisation of GAVI had been set up this way, or why WHO and UNICEF would have agreed to it. This section offers some possible insights into the development of this situation.

The United Nations operates on a relatively small budget; US$1.26 billion per year for the United Nations and US$10 billion for the entire system it oversees. For many years it has been in a state of "financial crisis" (UN 1999, p 42) and operating in deficit. Its operations are dependant upon the financial contributions of member states, and some have failed to pay their dues. In some cases this is due to poverty and budgetary constraints, but "others have withheld payments as a way to exert pressure on the UN or to make a political point" (UN 1999 p 42). The USA falls into this last category, with dues owed as of 31 Dec 1999 of US$1.17 billion. This is the most owed by any nation, as the next on the list was the Ukraine with a considerably lower figure of US$212 million (UN 1999). Bill Gates has privately donated to global immunisation nearly the entire amount owed by the USA to the United Nations, when the CVI, managed by WHO and UNICEF was struggling to maintain its services due to lack of funding. This gives emphasis to the question asked by Paulson:

> Once you decided to donate most of your foundation's resources to fixing problems in the global immunization network, why not just write checks and send them off to the United Nation's agencies, the World Health Organization and UNICEF, charged with this responsibility? Why create a whole new ballgame directed out of Seattle? (Seattle P-I 2002b)

There are many aspects to this situation, and some of the more important ones will be discussed. These include: the increasing involvement of the United Nations with transnational corporations; the reductionist perspective of western medicine and western medicine's penchant for 'quick-fix' solutions; the USA history of hegemony over technology, scientific advances and global politics, and the technophile background of Gates.

13.6.1 THE UNITED NATIONS AND TRANSNATIONAL CORPORATIONS

The United Nations displays a growing trend towards involvement with business in general and increasingly with transnational corporations:

> By 1998 . . . the climate between business and the United Nations had changed so radically that the U.N. secretary-general and other U.N. officials had begun to meet regularly with business leaders in gatherings sponsored by the International Chamber of Commerce (ICC), the World Business Council on Sustainable Development, and other international business organizations. (Millen, Lyon & Irwin 2000, p 238)

A significant motivator for this change in policy is likely to have been economic expediency. As outlined above, the United Nations has been operating in deficit as a result of dues unpaid by nation members. Of the 100 largest economies in the world 49 are nations and 51 are corporations (Millen, Irwin & Kim 2000a). Corporations represent a lucrative source of capital and are interested in contributing funds towards United Nations programs partly as a public relations exercise, but more importantly as a means of extending and protecting their market interests. The President of the ICC intends to

> . . . bring together the heads of international companies and the leaders of international organizations so that business experiences and expertise is channelled into the decision-making process for the global economy. (Maucher in Millen, Lyon & Irwin 2000, p 239)

Many non-government organizations (NGO's) and environmental protection groups have expressed concern that the collaboration between the United Nations and

business is being driven by the corporate leaders (see for example Colgan 2002; ESW 2002; Kim et al 2000; SCUK 2002). The corporate leaders have long been uneasy with the close association between the United Nations and “increasingly outspoken labor, human rights and environmental groups” (Millen, Lyon & Irwin 2000, p 239). Many NGO’s from around the world are, in fact, organizing to place limits on the political powers of corporations as they are concerned about their capacity to exploit the economies and resources of developing nations (Millen, Irwin & Lyons 2000).

This is relevant to immunisation because, as outlined in Section 13.2.3, GAVI has gone much further than the EPI in forming a collaboration between WHO, UNICEF, USA government agencies such as the FDA and CDC, and business leaders. It has done this to the point where it has been criticised for having corporate interests on its governing boards. Its agenda is specifically to introduce the more expensive combination vaccines into the schedules of developing countries. The goal of EPI, was to extend the reach of basic immunisation to the populations who do not have sufficient access to the traditional vaccines, and independent reports conclude that GAVI has given insufficient consideration to the resources and structures required to achieve this outcome (SCUK 2002, Whitehead & Pasternak 2002). Despite persuasive rhetoric, and the involvement of many eminent international figures (GAVI 2002), it is possible to view the actions of GAVI as being guided by the corporate interests of the vaccine manufacturers. Otherwise, Gates could simply have donated his funds to WHO and UNICEF and left the locus of control in Geneva.

13.6.2 BILL GATES - TECHNOPHILE AND PHILANTHROPIST?

Gates has initiated philanthropic projects since 1995 and, partly because of the scale on which he works, each project has been subject to some criticism. In 1995

he gave away US$60 million worth of computer software, and in 1997 he gave more than US$90 million to provide computers for libraries to make computers and the Internet more accessible to the poor. Both gestures were criticised for being thinly disguised moves to expand Microsoft's market share.

Ironically, now that he is involved in immunisation, some are saying he should be helping to provide computers and internet access for developing nations. In this context his commitment to improving world health standards is certainly more pertinent. He should also be credited for his degree of involvement in The Bill and Melinda Gates Foundation. "A lot of wealthy families set up these foundations just to shelter money" (Seattle P-I 2002b, p 1), but Gates is actively involved in the decision making and public advocacy. This has reduced his tax advantage by 20% (Seattle P-I 2002b).

Gates has chosen to support immunisation in particular over other equally, if not more important public health measures. His history of involvement with technology and large business corporations provides an insight into this decision. Of the possible areas of public health in which he could have become involved, immunisation provides the greatest opportunity for him to operate in a sphere that involves complex technology, large investments, and transnational corporations. It allows him to operate in a sphere in which he is comfortable.

Most of the basic public health measures such as the provision of safe water, improved nutrition and family planning require an initial input of funds and expertise to establish resources and procedures. To be successful they should ideally be set up in such a way as to be easily managed by the local population, providing them with autonomy (Colgan 2002). In contrast to this, immunisation requires the ongoing involvement of large industry, complex technology and the expertise of

western medicine. It is an area that requires the continued provision of aid and technological support. It guarantees the continued involvement of industrialised nations in the governance, policy formation and economic decisions of developing nations. Few nations, industrialised or developing, would ever be autonomous in their provision of immunisation services.

13.6.3 THE REDUCTIONIST PERSPECTIVE OF WESTERN MEDICINE - THE PENCHANT FOR A QUICK-FIX

Medicine in the western tradition, as with western science in general, has a long history of taking a reductionist and technological perspective on disease:

> . . . the approach to biology and medicine established in the seventeenth century was an engineering one based on a physical model; the consequences are even more conspicuous today, largely because the resources of the physical and chemical sciences are so much greater . . . medical education begins with the study of the structure and function of the body, continues with examination of disease processes and ends with clinical instruction on selected sick people. Medical service is dominated by the image of the acute hospital where the technological resources are concentrated . . . (McKeown 1979, p 7)

While some progress has been made in the awareness of environmental and behavioural determinants of non-infectious diseases, treating infectious disease is still largely viewed in terms of correctly identifying which pathogen is present and administering the appropriate drug based therapy. Immunisation, or providing exposure to attenuated, inactivated or surface molecules of the pathogen is seen as the primary preventative measure. The vast mass of scientific literature pertaining to immunisation is in accordance with this view, that:

> . . . improvement in health depends essentially on knowledge of the body and its diseases, applied through personal medical intervention in the form of immunization and therapy . . . (McKeown 1979, p 10)

McKeown makes a detailed analysis of the incidence and mortality from various infectious diseases from the time regular population statistics were first kept in the seventeenth and eighteenth centuries until the present. He provides evidence that a significant and long-term trend in the decline of infectious diseases and improvement in health in general was evident long before the advent of vaccines and drug therapies

> . . . the modern improvement in health was initiated and carried quite a long way with little assistance from science and technology . . . (McKeown 1979, p 10)
>
> Many medical scientists believe that the control of bacterial infections is based on knowledge of infectious diseases derived from basic research and applied largely . . . through immunization and therapy. . . [Evidence provided in earlier chapters arrives] at quite a different conclusion: that these measures had little effect on the death-rate before 1935 and since that time have been less important than other influences. (McKeown 1979, p 161)

Improved nutrition is postulated as a significant underlying factor, citing research that indicates that a malnourished person is more susceptible to infection, and that infectious diseases

> . . . have an unfavourable effect on nutritional state, and the interaction between disease and malnutrition leads to a vicious cycle with is characteristic of poverty and underdevelopment. (McKeown 1979, p 61)

He points out that this is as true for conditions for which immunisations exist, as for those for which they don't, and questions whether infectious diseases can be controlled by vaccination in a malnourished population. This view is reinforced by a report issued by WHO:

> We have given too much attention to the enemy and have to some extent overlooked our own defences . . . For the time being, an adequate diet is the most effective "vaccine" against most of the diarrhoeal, respiratory and other common infections. (Behar 1974, p 29)

This is in line with the comments made on nutrition in Section 13.5. However, despite the fact that this view was expressed 25 years ago, the primary measure for prevention of infectious disease is still seen to be immunisation. In fact Gates is

going even further and proposing immunisation as a potential cure for poverty (Seattle P-I.com 2002b).

Immunisation has maintained its attraction because it is the epitome of industrialised medicine. In line with many other disease treatments and preventative measures developed by industrialised nations, it is

- a quick-fix solution – a short series of injections provides protection.
- proactive and publicly visible – the government is seen to be addressing health problems.
- technologically complex to develop.
- employs many scientific researchers, health professionals and administrators.
- represents considerable profits to large corporations.
- a lucrative source of future research and health interventions.
- relatively easy to collect and analyse statistics on use and relative disease incidence.
- secures the ongoing involvement of industrialised nations in the political and economic affairs of developing nations.

Above all it suggests that the problem of infectious disease is being constructively addressed. This is much simpler than attempting to deal with the complex social and economic factors that were outlined in Chapters 11 & 12 that are increasingly being recognised as the true underlying causes of poor health. Instituting an immunisation program is simpler than addressing issues such as: increasing inequalities in wealth within and between nations, the effects of neoclassical economic policies on both developing and industrialised nations, the role of transnational corporations in exploiting labour and resources for profit, the need for governments to provide secure access to basic resources such as adequate nutrition, clean water, reasonable wages and working conditions, the need to build and support community solidarity and personal self-esteem.

If Gates was serious about alleviating poverty and infectious disease in both developing and industrialised nations, there is much to be said for the perspective

that he would be using his power and influence to address issues such as these. In a genuinely holistic approach to public health care, immunisation would then fill its proper place as a useful preventative measure for some infectious diseases.

13.6.4 THE HEGEMONY OF THE USA

The USA has a long history of technological and cultural hegemony. It is beyond the scope of this thesis to provide a detailed analysis of the historical, sociological and economic factors that have contributed to this, however it is worth noting that the USA is a dominant force in medical technology and research in general, and in the domain of immunisation in particular (Corless, Nicholas & Nokes 2001; Gaye 1998)

Most of the highly regarded scientific journals that regularly report on immunisation research are from the USA, for example *Vaccine*, *Journal of the American Medical Association*, *The New England Journal of Medicine*, *Pediatric Infectious Diseases Journal* etc. There is considerable pressure for foreign nationals to publish in English in these and other English language journals (see for example the debate between the French and the US over self/non-self in Chapter 3). The USA is also the base for the main scientific information sharing databases such as Medline and Web of Science. So on an information level, regardless of its own research output, the USA is a locus of control for immunisation research. This is complementary to its increasing dominance in the formulation of global immunisation policy and programs (as outlined in Sections 13.2.3 & 13.3).

Other industrialised nations have equivalent resources and expertise. For example the United Kingdom hosts the equally respected journals *The Lancet* and *The British Medical Journal* which also report frequently on immunisation research. Other nations such as Australia, Belgium, Denmark, France, Finland and Korea are

involved in research and development or are hosts to transnational corporations who are involved in these activities (WHO 2002b).

Hence, despite the fact that there are now relatively few US owned corporations involved in vaccine research and development (see Section 13.4.1), and despite the fact that they do not have a monopoly on global research and that equivalent resources exist elsewhere, the USA maintains a dominant position in the domain of immunisation. This is relevant to the situation in Australia. Australia is not only a political ally of the USA. Since World War II, Australia has increasingly followed the USA in matters of culture, policy, and technology (Carruthers 1998). The Australian situation with regards to immunisation will be discussed in Chapter 15.

13.7 CONCLUSION

There are many facets to the current global situation regarding the development of policy and provision of finance for immunisation programs. They include the complex interplay of different departments of the United Nations, particularly WHO, UNICEF, the World Bank and the IMF as well as many NGO's, transnational corporations who research, develop and produce vaccines, smaller corporations who produce vaccines and the governments of all involved nations. The development of international immunisation policy, and the dissemination of relevant information is being increasingly influenced by transnational corporations and both government and private agencies from the USA.

The production and marketing of vaccines sits within the domain of high investment, technologically complex western medicine and the dominant trend is away from the simple cost effective traditional vaccines towards increasingly complex, expensive combinations. Set against a global economic trend of increasing inequality in income both within and between nations, immunisation is

mirroring this trend. Despite rhetoric to the contrary, the transnational corporations are gradually phasing out the production of traditional vaccines and increasing their emphasis on producing combinations at a higher cost.

Previously all nations had similar immunisation schedules and used the same vaccines. Now there is increasing disparity in the schedules between developing and industrialised nations, making immunisation yet another area of growing inequity (Batson 1998). The attempt by GAVI to address this issue has been fraught with difficulty, and only highlights that immunisation is set to become another area of health inequality, leaving the root causes of this inequality, once again unaddressed.

> Technology and its shaping has to do with the historical, the economic, the political, and the psychological, as well as with the sociological. (Bijker & Law 1992, p 5)

This is true of immunisation. Although couched in terms of the highest ideals for improvements in global health, the development and implementation of vaccine technology is driven by a host of political and economic agendas. Although presented as a means of alleviating poverty and inequity in health within and between nations, evidence has been presented that it may, in fact, serve to exacerbate this situation.

CHAPTER 14

EPISTEMOLOGY AND ETHICS

14.1 INTRODUCTION

A study of the epistemology, “the method or grounds of knowledge” (Sykes 1976) of immunisation raises ethical issues. This chapter examines the claims to the certainty of scientific knowledge pertaining to immunisation, the ways in which information is obtained, filtered and constructed, and the treatment of those who dissent from the prevailing scientific view. This chapter will also discuss ethical, political and public health issues that are raised by a critical analysis of the epistemology of immunisation.

14.2 IMMUNISATION AND THE CERTAINTY OF SCIENTIFIC KNOWLEDGE

Scientific knowledge, based on empirical evidence, is popularly regarded as being the most certain knowledge that we can have of the physical world:

> "Science" conveys an imprimatur of certainty . . . In general, non-scientists tend to overestimate the degree of certainty attached to a scientific result. This is not surprising when a phrase like "scientifically proven to" is routinely used to mean "100% sure". This misunderstanding is extremely harmful to the task of accurately communicating real scientific developments because it results in the perception of true certainty whenever anything "scientific" is being discussed. This misrepresentation of the certainty of results may occur even when a journalist includes multiple caveats in the report. (Garret & Bird 2000, pp 437-39)

The medical profession, politicians and other stakeholders, however, utilise this perception when advocating immunisation to the public. A handbook for immunisation providers on how to deal with objections to the procedure states:

> Immunisation has been repeatedly demonstrated in both research trials and in measurements of efficacy made in the field to be one of the most effective medical interventions we have to prevent disease. (Hall & O'Brien 1998, p 1)

In handbooks produced for the public, statements about immunisation are presented as simple and incontrovertible facts, for example:

> <u>How does immunisation work?</u>
> All forms of immunisation work in the same way. When someone is injected with or swallows a vaccine, their body produces an immune response in the same way as it would to a disease, but without the person getting the disease. The body then keeps proteins called antibodies circulating in the bloodstream to fight against the disease should it appear. Then if the person comes in contact with the disease in the future, the body almost always makes an immune response fast enough to prevent the person getting sick. (Commonwealth Dept of Health, 1995, pp 6-7)

As has been demonstrated previously in this thesis and in these quotes, which are typical of the type of information disseminated to both immunisation providers and the public, neither of these statements attests to the complexities and debate regarding efficacy and outcomes. In particular:

- Research trials and efficacy studies suffer from significant design faults, and problems with measurement parameters, data collection and analysis. (Chapters 7- 9)
- Immunisation may be an effective *medical* intervention to prevent disease, but it is not necessarily the most effective preventative measure per se. (Chapters 11-13)
- All forms of immunisation do not work the same way, there are variations between viral, bacterial, live, attenuated, inactivated, whole cell, subunit and combination vaccines. The body responds differently to each and some reactions may counteract others. (Chapters 2-7)
- Antibodies do not necessarily circulate in the bloodstream, in fact there is no consensus on how immunological memory works. Antibody levels do not correlate with protection. (Chapters 6 &8)
- The person may be vaccinated and still get the disease. (This is admitted later in the same booklet on p 32). “Almost always” is an exaggeration of the degree of protection, which varies considerably with the vaccine and health status of the recipient. (Chapters 2-7, 11-13)

As has been demonstrated in previous chapters, the scientific knowledge with respect to immunisation is not as certain, objective or universally verifiable as medical discourse suggests. The evidence presented here supports the perspective that:

> Scientific knowledge is generated to serve certain purposes . . . it always incorporates values, and hence always is selectively useful to certain groups. (Martin 1979, p 75)

Issues that need to be examined in relation to this situation include the way in which information about immunisation is collected, processed and imbued with credibility, the power structures within the scientific, medical and political communities which underlie this process and the influence of the internet and public access to information.

14.3 THE COLLECTION OF INFORMATION ABOUT IMMUNISATION

14.3.1 PROCESSES THAT CONTROL AND INHIBIT THE COLLECTION OF INFORMATION

> Technologies are not purely technological . . . they are heterogenous . . . they embody social, political, psychological, economic and professional commitments, skills, prejudices, possibilities and constraints. (Bijker & Law, p 7)

It was shown in Chapter 13 that the development and implementation of the technology of immunisation is influenced by many factors, and discussed economic and political considerations in particular. This section examines the various ways in which scientific data is selectively acquired to provide support for both national and international policies on immunisation.

> Certain purposes will be served if the range of scientific attention is limited in a certain way. Due to the structure of society and the current aims of scientific practice, scientists may find it natural to limit their attention appropriately. Then after the choices are made, principles may be drawn up to explain and justify the choices. (Martin 1979, p 76)

Information about the safety and effectiveness of vaccines is largely obtained from scientific studies, both biological and epidemiological, which vary in design, rigor and usefulness (see Chapters 7-9). As they are largely conducted by companies seeking approval for new vaccines, their scope to predict any anomalies in reaction that may occur when the vaccines are administered in real-world, suboptimal conditions, or to detect unusual or infrequent adverse events is limited (Clemens et al 1996). The type of information received from these trials is limited and controlled in various ways.

One limitation is that researchers are unlikely to take detailed personal histories of the research participants and their particular medical and social status, either due to constraints of time or funding, or because the significance of this information is not recognised. Very few studies include any data on factors such as parent age, health, education, area of residence, occupation, socio-economic class, dietary patterns, nutritional status, personal habits such as smoking, or stress levels, and yet these are all relevant to the ability of the child to mount an appropriate immune response to a vaccine, and to determine susceptibility or resistance to disease in general (Clemens et al 1996; Pilgrim & Rogers 1995).

Similarly these studies only examine the frequency of a limited range of physical responses that have already been defined as adverse events. These correlate with responses already outlined in the guidelines of government regulatory bodies such as the NHMRC in Australia, or the FDA in the USA, and in vaccine product inserts produced by the vaccine manufacturers. They show a great deal of similarity between vaccines (eg NHMRC 2002). Researchers often seek this information in questionnaire form for easy analysis. Unexpected or infrequent adverse events are either not recorded, not reported, or do not make it into the published article for comparison with other studies.

> Vaccine safety is an important issue for such trials, but efficacy trials usually focus only on adverse effects that are expected on the basis of earlier studies, that occur shortly after vaccination and are frequent, and that are easily measured with symptom questionnaires and other available instruments. (Clemens 1996, p 391)

.

In these ways researchers bring their preconceived ideas about what they want to find out to the design of the research. In so doing there can be a screening of information which could have significant bearings upon determining the causes of unexpected or infrequent adverse events, or upon longer term health consequences for the recipients.

The potential to correct these shortcomings during follow up trials is generally lost for the following reasons. Conventionally, the Phase III trials done prior to licensure of a vaccine focus on proving vaccine safety, whereas Phase IV trials, conducted after licensure are meant to focus on determining vaccine efficacy (Clemens 1996). In reality Phase IV trials are rarely conducted. As Clemens observes:

> Funding for phase IV studies, from either industrial or nonindustrial sources, is minuscule in comparison to that allocated to phase I through III studies, since phase IV studies are usually not mandated for continued marketing of an already licensed vaccine. The lack of regulatory requirements for such studies also means that they tend to be undertaken in a sporadic and opportunistic fashion by investigators with specific research interests. (Clemens 1996, p 394)

There is one further opportunity to gain access to broader information from the public regarding their direct experience of the effects of a particular vaccine, or combination, on the recipients. This is the existence in some nations of government funded adverse event reporting systems, such as the Vaccine Adverse Event Reporting System (VAERS) in the United States, and reports to the Australian Drug Reactions Advisory Committee (ADRAC) in Australia. Once again, protocols are in place to make sure the information received fits within predetermined guidelines (NHMRC 2000a). However, as a medical practitioner has pointed out:

> When does a series of individual observations from families with affected children count as evidence if each one is dismissed as an isolated incident? (Heller 2001, p 838)

Data on adverse events is simply recorded and reported in statistical form. An extensive literature search failed to find any studies into the reasons why some children have adverse reactions to vaccines and others don't, or on why they experienced that particular adverse event rather than another.

In both Australia and the U.S., notifications may only be provided by the health professional, usually a medical practitioner, who administered the vaccine. In the USA reporting of events by providers and manufacturers is required by law for reactions listed in the "Table of Reportable Events Following Immunization", other reports are voluntary (VAERS 2003). The situation in Australia varies between states (see Section 15.3). This variation compromises the capacity to build an accurate nationwide assessment of reactions to a particular vaccine, or to analyse wider social factors that may be impacting on immediate or longer term responses.

It is well accepted that even in the United States where reporting of adverse events is legally required, only about 10% of events are ever reported (Orenstein & Bernier 1990; Ward 2000). Reasons given for this include time constraints on providers,

provider's fear of litigation, reluctance of providers to acknowledge or report the occurrence of adverse events because they do not wish to undermine public confidence in immunisation, fear of reprisal from colleagues, or genuine disbelief that reactions occur (McFarlane 1995; Taycare 1997).

> [After an incidence of immediate and severe anaphylactic shock] When I requested copies of Graham's medical records for us to keep at home, we were shocked to see (or rather NOT see) no mention of his reaction and treatment listed anywhere in his records fro that visit or anywhere else. . . He made NO mention of our son's life-threatening vaccine reaction in our son's medical records. When I brought this "oversight" to his attention, he actually asked me what I wanted him to say!! (Anonymous 2003a, p 2)

> [After a prolonged hypotonic/ hyporesponsive episode, choking fits and "two hard baseball sized black and blue lumps" on the child's legs]The doctors office was refusing to report her reaction to VAERS, or even to write it down in her chart !!!!! I was furious, so I reported it myself. (Anonymous 2003b, pp1-2)

In Australia this was verified by a study in South Australia where adverse event reports were "encouraged from all vaccine providers, *recipients* and medical practioners" (Gold et al 1998, p 40, italics mine). They found that the rates of accepted notifications were "7-13 fold greater than those reported nationally" (Gold et al 1998, p 41). These figures apply to the 79 reports that they accepted after they had screened out ones that did not fit the notification criteria. They actually received 314 notifications - nearly four times that number. These figures give some insight into the extent of adverse events that are never reported and cast doubts on the validity of the adverse event statistics widely publicised to promote vaccine safety and allay public concerns. To their credit, between 1997 and 2000, the Australian authorities (primarily the NHMRC and ADRAC) lifted time constraints, broadened the parameters of acceptable notifications and are moving towards a policy of open disclosure (NHMRC 1997; NHMRC 2000a; Safety and Quality 2002). This will be discussed in more detail in Section 15.3.

14.3.2 SCIENTIFIC VS LAY KNOWLEDGE

14.3.2.1 Knowledge and the biomedical perspective

There is an inherent contradiction in the notion of a medical science. In designating itself a "science" and utilising the associated perceptions of credibility and certainty (see Garrett & Bird 2000), medicine seeks to establish

> . . . a set of laws and universal judgements, which like all sciences aims to be nomothetic and absolute. (Rollin 1979, p 294)

Its fundamental perspective is widely characterised in the critical literature as "mechanistic, technological . . . and reductionist" and "tend[s] to be limiting and dehumanising" (Rothenberg 1979, p 289). This works in direct contradiction with the object of medical science, which is the

> . . . unique. . . the individual in his or her particularity. An over-emphasis on medicine as a *science* (value-free by implication) leads to tragic results for patients who do not fit a theoretical mould. . . Individual differences do matter. (Rothenberg 1979, p 294)

It is not only individual differences that matter, but also the individuals:

> Over the past fifty years, medical education has grown increasingly proficient in conveying to physicians sophisticated scientific knowledge about the body and its aberrations, and technical skills to implement that knowledge. Yet at the same time it has failed to give corresponding attention to the scientific understanding of human behaviour and of the psychological and social aspects of illness and patient care. (Engel 1979, p 257)

These issues are particularly relevant to immunisation, where both government policy and the behaviour of immunisation providers have a history of being coercive, aimed at mass population compliance, and with a limited consideration given to the rights, preferences and concerns of individuals (see for example Dare 1998; Nokes & Anderson 1991; Pellegrino 1984).

The prevalence of the biomedical perspective has contributed to the neglect of the 'grey areas' of immunisation: the issues of vaccine failure and adverse events, and the dearth of research on factors contributing to these phenomena. It also lies behind the neglect of the influence of broader socio-economic conditions on the

health of individuals, populations and their relative susceptibility and resistance to disease. It has been proposed that this reductionist view, in relation to immunisation, has had a limiting effect on the ability of health workers to place infectious disease prevention in a broader context:

> . . . the political over-reliance on [mass childhood immunisation] as a source of disease prevention deflects health workers (and dependent parents) from utilizing other sources of legitimate knowledge about risk to infection. The latter include the age, nutritional status, type of child care, constitution and social class of the child in question. (Pilgrim & Rogers 1995, p 67)

This perspective has led to the neglect of a large and valuable source of information, that is the personal experiences of the recipients of immunisation, and a corresponding technology driven focus on service provision that does not always take account of consumer needs (Banta 1995; Egdahl & Gertman 1978; Newsom-Davis & Weatherall 1994).

> The health care delivery system and its financing are organized with the assumption that the doctor – that is, the laboratory – is right and the patient is wrong . . . as long as the biomedical model prevails, unscientific and simplistic solutions for the complaints of patients will be promoted. (Engels 1979, p 262)

14.3.2.2 Knowledge and the lay community

The frequency and range of adverse events, and broader contributing health factors are examples of information that disseminates informally amongst consumers, particularly the mothers of small children who are currently undergoing their immunisation schedule from birth to five years. The reluctance of some medical practitioners to acknowledge the occurrence of an adverse event by agreeing to define it as such, or to report adverse events even when requested to do so by the parents, becomes well known and may lead to dissatisfaction or mistrust of the procedure (AVN 1998; Rogers & Pilgrim 1995). These types of consumer experiences have led to the establishment, in many nations, of consumer run immunisation information services and more recently websites,

which disseminate scientific information about vaccines on request, and also collate accounts of consumer experiences. Examples of these are the Australian Vaccination Network (AVN 2003), the Immunisation Awareness Society in New Zealand (IAS-NZ 2003) and the National Vaccine Information Centre in USA. Formally it is the general practitioners and other immunisation providers who are charged by the government with the role of disseminating information on immunisation. The fact that consumers in many nations have felt the need to establish their own information services attests to a significant degree of dissatisfaction with the nature and quality of this information provided by government health departments via immunisation providers.

The following are typical of the many stories that are accessible through these consumer groups that demonstrate the reluctance of immunisation providers to acknowledge reactions, ranging from crying to death, that the parents claim good reason to believe have been caused by immunisation:

> (Of a previously healthy 8 week old baby who screamed and cried non-stop and developed severe gastric problems immediately following immunisation and died five days later:)
> [The doctor] admitted he gave the shot to Dylan without obtaining informed consent . . . admitted he did not correctly fill in the immunisation record with the batch number of the vaccines. . . knew of regulations to report reactions but did not think it necessary to report as he considered there was no possibility of the vaccine causing the reaction. [The death was recorded as SIDS] (AVN 1998, pp 15-22)

> (Of a child who developed chronic glue ear and throat infections after the 3rd vaccination visit :)
> When the nurse gave Andy his injection she remarked that it looked turbid, but injected it anyway. The doctors said there was no link between vaccination and his health problems. (AVN 1998, p 38)

> On day three after her vaccination, I took her to two different doctors about her flapping arm and no vocalisation, and both told me that it was a phase she was going through, that had coincided with the injections, and unless she had an extraordinarily high temperature, not to worry. (AVN 1998, p 55)

> My children are three years apart, after each of them had their 12 month MMR vaccine their skin peeled. It started with their hands. They went all red and the skin peeled off their whole body. The doctor refused to report it, he

> said it was probably an allergic reaction to something else. (Anonymous 2001, personal communication)
>
> With his first triple antigen he screamed for four hours. With his second triple antigen he had a high fever, went totally crimson all over and screamed plus doubled up for about 4 hours. Then with his third triple antigen he had a high fever, vomited, cried non-stop for a full day, went crimson and doubled up. Now I reported this to my doctor and he told me that this was normal. But with my two other children I never had these reactions. (AVN 1998, p 68)

In these accounts are reactions, such as the high fever, unusual rash, and floppy arm which should be reported, and in Australia are now reportable. However, it is clear that the doctors concerned did not regard them as adverse events, or as worth reporting.

There are also many cases reported by parents through these consumer groups of children who were well prior to the immunisations, who have reacted severely and died within a few hours, and the deaths have been reported as Sudden Infant Death Syndrome (SIDS) with no mention made in the medical records of the immunisation as a possible causal or contributing factor, for example:

> The doctors did not want to talk about her death being related in any way to the vaccine and one after the other, refused to answer our many questions. [and in contradiction to this, they also said] . . . that vaccines were for "the greater good". I was even told that loss of life through immunization was "expected" in the war against disease, but these losses were considered to be at "acceptable" levels. . . . The coroner finally told us months later that the cause of death was determined to be "SIDS" meaning "no known cause" and refused to release a copy of the autopsy report to us.
>
> It took almost a year for us to obtain this report and to our great horror, we realized that the autopsy summary was copied directly from the vaccine product monograph under the heading "Contraindications" . . . There was no toxicology testing performed and the pediatrician never filed an adverse vaccine reaction report with the health authorities. I later learned that most vaccine-induced deaths in this country are listed as SIDS, and that SIDS statistics are NOT included in vaccine adverse reaction data, even if a child dies only a few hours after receiving inoculation. (Colebeck 2003. p 3)

> Amanda went to her doctor for her vaccinations. On that very day, the doctor claimed that Amanda was "perfect". [she reacted to the vaccine and died a few days later] Amanda's death was declared as SIDS. . . Can you believe that the investigating staff . . . would go through the effort to

> question two loving parents on the worst day of their life, yet would not even bother to ask if Amanda had recently received any medications or shots that could have caused a bad reaction: Why didn't they ask? . . . My guess is that if it isn't documented, no one will really know and no one can use the statistics to build a solid case.
>
> In October 2000 a very good friend of mine lost her one-year old grandson within a week of receiving his MMR vaccination. His doctor told his mother that he was in perfect health the day he gave him this injection. The details of this case are very unsettling, and of course vaccination is not listed as the cause of death for this child either.
>
> . . . These two deaths of perfectly healthy children have been completely dismissed of any possibility of being caused by vaccination. I have to wonder how many other possibilities have been eliminated from the statistics I have read. (Keller 2003, p 2)

In a community, these experiences become part of a lay knowledge about the potential adverse events and contradictions in information provided about immunisation and the attitude of the medical profession. The medical profession has ignored this knowledge system at its peril. As Daniel argues:

> Central to professional identity is the command of a field of abstract, complex knowledge that practitioners interpret and apply in the interest of their clients. This knowledge base is a powerful material resource which a profession monopolises. (Daniel 1990, p 36)

To maintain its status and credibility, medicine relies heavily upon its knowledge and expertise. This position has been threatened recently with the increasing ease with which the public can access scientific and medical information via the internet. Scientific and medical knowledge is no longer as privileged as it used to be and

> The growth of a more sophisticated public means that the question of the validity of professional knowledge becomes more rather than less relevant. (Turner in Daniel 1990, p 36)

Prior to this development, non-uptake of immunisation was (and still is) generally regarded as irrational:

> Those resisting MCI [mass childhood immunisation] in the surgery are sometimes deemed to be suffering from neurotic anxiety. In studies on reasons for low uptake, parental concern about the safety of vaccines are (sic) discussed in terms of 'mythical', 'parentally perceived', and 'false' contraindications. (Rogers & Pilgrim 1990, p 104)

Now it is far easier for interested members of the public to obtain scientific information of the same quality as that provided to medical practitioners, and it is readily apparent that:

> There is a recognition within the medical literature of the uncertainties and failings of vaccination, which do not appear in publicly available literature about vaccination. (Rogers & Pilgrim 1990, p 104)

Those who are pro-choice or anti-immunisation are now able to contest the issues on the same scientific grounds as had previously generally been the preserve of advocates. Immunisation has long been a contested issue (see for example Swales' (1992) account of the Leicester Anti-Vaccination League of 1869 and their protests against smallpox vaccination), but it is increasingly being contested on the grounds of scientific validity. Increasingly, both sides are using the same resources and quality of information, which is precisely why this thesis has endeavoured to place the whole debate into a wider framework.

Evidence has been presented of a divide between scientific and lay knowledge regarding immunisation, as there is also in other areas of medical endeavour (see for example Richards 1991). It would appear that much can be gained from a constructive attitude towards addressing the issues of concern outlined above. On one hand the medical practitioner's traditional reliance on the sanctity of expert scientific knowledge is under threat as consumers and interested members of the public now have sufficient access to scientific research and journal articles to appreciate the limitations and contradictions within this preserve.

> . . . she did not trust doctors' opinions over vaccines, because they tended to express certainty in areas that were fraught with uncertainty. (Rogers & Pilgrim 1995, p 103)

This can be addressed with a more open attitude, as is recommended in Health Department literature to medical practitioners here in Australia:

> Mere logical demonstration of the weakness of arguments against immunisation will not be sufficient, and a positive, caring attitude is essential. (Hall & O'Brien 1998, p 2)

On the other hand, the valuable resource of consumer experience and first hand knowledge of the effect of immunisation is undervalued and filtered out of the scientific domain. The problems with limitations on study design and controls on information collected in scientific studies are exacerbated by disinterest, denial and reluctance to report on the part of medical practitioners. This has led to comments like the following:

> The whole time I was treated like a first time mother overreacting, although a mother can always tell when something is wrong. But instead of listening we were pushed out the door. (Hewitt in AVN 1998, p 18)

In fact parents have much useful information to offer. In his research on measles, Aaby observes that:

> It should be noted that mothers in many instances have had a better perception of the epidemiological reality . . . and they have an appreciation of vaccines which clearly goes beyond prevention of specific diseases and suggests that a vaccine may have non-specific effects. (1995, p 684)

It is possible that much would be gained from the scientific and medical community approaching consumer experience with more interest and respect. This policy is currently being pursued by the NHMRC (2003) Consumers may then experience increased confidence in the medical profession and immunisation as a procedure, and the researchers would gain access to much useful information.

14.4 THE PROTECTIVE ATTITUDE OF THE MEDICAL PROFESSION TOWARDS IMMUNISATION AND SOME REASONS FOR THIS

14.4.1 PROTECTIONISM

The medical profession is protective of immunisation. It has been shown how the experiences and concerns of the lay public are excluded, in addition to this, strategies are employed to “marginalize” concerns raised from within the scientific community itself (Dew 1999, p 382).

> The reasons why such concerns are marginalized could be many, ranging from the powerful role that pharmaceutical companies play in such processes, to the ideology of biomedicine. Feyarabend argued that one characteristic of scientific research was that any theories competing with the accepted one are ignored, even if all the relevant facts fit the alternative theory . . . Such taboo reactions occur when dissenters question the efficacy of vaccines. (Dew 1999, p 382)

Three examples will be discussed that show the range of strategies used to protect the status quo. The first is an example of the practice of publishing one or more overtly pro-immunisation commissioned articles following a single article that provides a balanced view of the pro-choice and anti-immunisation arguments or encourages debate of the issue in some way. The second example shows the patronising way in which pro-choice and anti-immunisation proponents can be regarded. The third example demonstrates how even highly regarded scientists are treated by their own profession if they publish any results that raise safety concerns or broader health issues with regards to immunisation.

1. Publication of chaperone articles.

It is an accepted practice in scientific journals to publish chaperone articles when dealing with a controversial topic. In this tradition, even the most conservatively worded article that raises concerns about immunisation, or simply outlines the views of others who voice concerns, is accompanied, usually in the same journal issue, by at least one and sometimes several, solicited articles which voice outrage that doubts should be expressed about the procedure. For example the article by Rogers and Pilgrim quoted above, which is more outspoken than most articles concerning ethical and policy issues, contains statements such as:

> Literature on immunisation is often presented in an emotive way, which suggests that fine lines exist between information, reasonable moral pressure and coercive propaganda. This raises doubts over how informed the average parents are when entering their child for a course of immunisation. (p 106)

And concludes in part:

> . . . those who oppose MCI [mass childhood immunisation] may not hold 'the truth' about the safety, efficacy and administration of vaccines, but they certainly have reasonable grounds for bringing these into question. (p 106)

This is immediately followed by an article which starts:

> It is extraordinary that, while childhood immunisation has been the most cost-effective health intervention of the twentieth century, its value and necessity are still challenged. The impact of current vaccines, and the virtual disappearance of previously common childhood diseases in many developed countries, has bred a dangerous complacency in some sections of the community. (Gust 1995, p 107)

2. The superiority of the scientific perspective.

Note the tone of the following excerpt from an article analysing the views of the pro-choice and anti-vaccination lobbies:

> Although the anti-immunisation case receives scant news coverage compared with normative or overtly promotional items on the value of immunisation, it is possible that even the small coverage it receives may be influential with non-immunising parents. . . News is selected in a manner quite unlike the peer reviewing process that determines whether original research is published in research journals. Journalists and editors selecting news are rarely qualified in any area of science or medicine and are therefore poorly positioned to judge whether the often elaborate quasi-scientific claims made by anti-immunisationists have any substance. More fundamentally, it is also naïve to assume that a primary criterion used to select news is that it should be capable of being interrogated by the highest standards of scientific evidence. (Leask & Chapman 1998, p 23)

It would seem to be implied here that although only 'scant' coverage is given to opposing views, the authors would prefer they be given no coverage at all, while being quite comfortable with the existence of 'overtly promotional items'. This is in

contravention of the democratic right to free speech and respect for alternative opinions which underscores our notion of a civil society. There is also heavy reliance here on the status of scientific knowledge and the process of peer review for scientific journals. This thesis has presented evidence demonstrating that this process is not as objective as portrayed (see for example Barnes & Edge 1982; Chalmers & Altman 1999; Charlesworth et al 1989), and it has been estimated that:

> . . . fewer than 5 percent of peer-reviewed journal articles . . . can withstand serious scrutiny, nor do they stand up well over the years. (Nobel 2000, p 107)

and an analysis of the most cited articles in the most reputable journals concluded that:

> a large proportion of the selected papers was fatally flawed with respect to experimental design and methodology, *ergo*, were scientifically unsound. (Warren in Newsom-Davis & Weatherall, p 129)

3. Harrassment and ostracism of a community member.

Members of the scientific community that raise concerns about immunisation can be subject to processes that could reasonably be described as harassment. This is justified on the grounds that their views may undermine public confidence in immunisation. A notable recent example of this is Wakefield's research into a potential connection between the MMR vaccine and irritable bowel syndrome.

Wakefield, and other members of the Inflammatory Bowel Disease Study Group at the Royal Free Hospital and School of Medicine in London had been publishing articles on a link between persistent measles virus infection, Crohn's disease and ulcerative colitis in *The Lancet* and other reputable scientific journals as early as 1994 (Ekbom et al 1994; Mazure et al 1994; Smith & Wakefield 1994). An article in 1995 (Thompson et al 1995a) discussing measles vaccination as a risk factor for Crohn's disease attracted some comments in a following issue of *The Lancet* , but in reply to criticisms Thompson et al claimed that:

> We reported the measles vaccination study for discussion by the scientific community, not only with many qualifications about its epidemiological aspects but also with great care not to excite media over-reaction. Indeed, we were commended by the UK Department of Health for our responsible attitude. . . We realised that the measles vaccination programme is of great importance to the community and the public health of the nation, but it would have been unethical to suppress this result because its preliminary conclusions were uncomfortable or inconvenient. (1995b, p 1364)

A series of further articles on the connection were published over the next couple of years (Montgomery et al 1997; Montgomery , Pounder & Wakefield 1997; Montgomery & Wakefield 1997; Thompson, Pounder & Wakefield 1995; Thompson et al 1996). However the controversy and extensive media coverage occurred when autism was brought into the equation.

> In eight children, the onset of behavioural problems had been linked, either by parents or by the child's physician, with measles, mumps, and rubella vaccination. Five had an early adverse reaction to immunisation. . . In these eight children the average interval from exposure to first behavioural symptoms was 63 days. (Wakefield et al 1998, p 640)

The article concluded:

> We did not prove an association between measles, mumps, and rubella vaccine and the syndrome described. Virological studies are underway that may help to resolve this issue. . . . We have identified a chronic enterocolitis in children that may be related to neuropsychiatric dysfunction. In most cases, onset of symptoms was after measles, mumps, and rubella immunisation. Further investigations are needed to examine this syndrome and its possible relation to this vaccine. (Wakefield et al 1998, p 640)

In part the media coverage was to blame for the degree of controversy generated, public concern over the rising incidence in autism, particularly amongst boys is possibly another contributing factor (Lee et al 1998). A number of articles were published soon after, refuting the evidence (see for example Fombonne 1998; Lee et al 1998; Peltola et al 1998; Thomas, Salmon & King 1998). The Lancet was criticised for publishing the article:

> The Lancet is a prestigious, peer reviewed journal with high public profile. The profession, journalists, the public and especially distressed parents of ill children suppose that a publication in your journal will be true. . . I think you will bear a heavy responsibility for acting against the public health interest which you usually aim to promote. (Beale 1998)

Wakefield et al were criticised for raising the issue:

> . . . such speculation may seriously damage important public health programmes, causing a decline in vaccine uptake and a rise in the target disease. We can now expect such damage to occur in many countries. We question the merits of publishing this particular study.
>
> Publication of this study is particularly tragic because WHO and all consulted national public health authorities agree that it does not alter in any way the continued recommendation to use measles-containing vaccines throughout the world. Current measles containing vaccines are highly safe and effective. (Lee et al 1998)

Subsequent articles published by Wakefield and colleagues were accompanied by referees reports, which were often supportive, and by articles voicing opposing views (see for example Earle 2000; Fletcher 2000; Hurley 2000; Wakefield & Montgomery 2000; Vere 2000). The controversy continued without much progress or resolution until the resignation of Wakefield in 2001:

> I have been asked to go because my research results are unpopular. I did not wish to leave but I have agreed to stand down in the hope that my going will take the political pressure off my colleagues and allow them to get on with the job of looking after the many sick children we have seen. They have not sacked me. They cannot; I have not done anything wrong. (Reuters Health 2001)

As can be seen from these three examples, there is a degree of protectionism around immunisation which has led it to be described as “an almost taboo corner of public health practice” (Stone 1995, p 113). He points out that:

> . . . the desirability of mass immunisation remains almost axiomatic among health care professionals [and] is an integral component of preventive medicine which can no longer avoid being subjected to ethical criticism along with all other forms of health care. (Stone 1995, p 111)

What is worth examining here are the reasons why the medical profession has taken this stance on immunisation, why so much effort is made to quieten or discredit dissenters or even just those wishing for an informed debate.

14.4.2 THE POLITICS OF PUBLIC HEALTH

The following statements are typical responses by senior medical practitioners to any debate over the safety or efficacy of immunisation:

> To those born before or shortly after World War II, it is hardly credible that a technology which has allowed the eradication of smallpox and the control of tetanus, diphtheria, whooping cough, poliomyelitis, measles, mumps and rubella, can have fallen from favour.
>
> When I was a resident medical officer I worked in an infectious diseases hospital which had a ward full of patients with paralytic polio, each encased in an iron lung, and separate wards for patients with measles, diphtheria or whooping cough. Twenty years later, as a result of immunisation, these diseases are so rare that some doctors graduate without having seen a case. (Gust 1995, pp 107-8)

> Immunization is the single intervention that has most dramatically reduced childhood morbidity and mortality. No longer do parents live in fear that their children will develop life-threatening paralysis from polio when they are at a swimming pool or the movie theatre in the summer. . . No longer are respirators standing by as a child, suffocating with the glue-like secretions of whooping cough, is brought to the emergency room late at night with his or her anxious parents trembling in a corner of the waiting room. We have entered a new era thanks to the development and widespread use of modern vaccines. (Katz 1999, p 2)

While not denying the intensity, horror and personal suffering involved in these accounts and others like them, they would appear to be based on two fallacious assumptions. The first being that immunisation is the only factor that has brought about a decline in these diseases, and the second being that things stay the same.

There is substantial evidence that rates of infectious diseases declined significantly before the advent of vaccines or other medical interventions. It has been estimated that 3.5% represents a reasonable upper-limit estimate of the total contribution of medical treatments to the decline in infectious disease mortality in the USA since 1900. This estimate includes all medical treatments, so vaccines would count for an even smaller percentage (Dew 1999; McKinlay, McKinlay & Beaglehole 1989). Also

> . . . for an understanding of infections it is unsatisfactory to consider separately an organism and its host. They are living things which interact and adapt to each other by natural selection. The virulence of an organism . . . is an expression of an interaction between a particular organism and a particular host. (McKeown 1979, p 45)

It is a well known fact that pathogens mutate, leading to variations of disease prevalence over time and between populations. For example:

> Poliomyelitis appears to have been a rare disease before the late nineteenth century. (McKeown 1979, p 101)
>
> The death-rate [of measles] fell continuously from about 1915; treatment (of secondary infections) has been possible since 1935; and mortality was at a low level before immunization was used [in the late 1960's]. (McKeown 1979, p 105)

A wide range of other factors play important roles in determining the prevalence and outcome of an infection. These include genetic, nutritional and general health status (including here the whole range of aforementioned socio-economic factors) of the host, modes of spread of the organism, pre-exposure either naturally or through immunisation, and the availability and nature of medical therapy.

It is fallacious to assume that if immunisation coverage were reduced then there would *necessarily* be a return to the epidemics of the past. Many factors are different, many factors are likely to reduce the incidence of disease, and some factors have the potential to increase it. To provide a very few of the more obvious examples, since the 1950's, in many areas of the world, there have been improvements in sanitation and availability of safe water, tighter health regulations on premises serving food to the public and greater public awareness of personal food hygiene. There are many more drugs, antibiotics and medical therapies for the treatment of disease. There are also problems with drug resistant strains of pathogens, increased concentrations of populations in large cities, international travel to assist spread of infection, and the potential for biological warfare and terrorism.

Even if immunisation programs were to decline, although the incidence of these few diseases may increase to some extent until an equilibrium is reached

(Gangarosa et al 1998), there is no evidence that the disease profile of an industrialised nation like the USA or Australia would return to pre-immunisation rates. The greatest areas of concern have shifted to lie with AIDS and other highly infectious pathogens brought in by international travel, to which populations have had little previous exposure.

There is also the issue that diseases for which vaccines have been developed have not all been chosen rationally on the basis of their epidemic severity. Some, such as rubella, have been developed partly because they have been possible as well as considered desirable, although the use of vaccines has raised questions about the future epidemiology of that disease:

> If the risk associated with infection increases with age, such a programme of immunisation at levels below eradication can therefore have perverse consequences . . . it carries the risk of pushing up the average age of those who do become infected with rubella towards those of child bearing age. (Anderson & May 1985, p 329)

Other vaccines are currently being developed with interests that far exceed the desire to simply improve the health of the affected population.

> In 1957, Dr Paul Russell of the Rockefeller Foundation, in a report to the U.S. International Development Advisory Board, reiterated the explicit interconnection of malaria [vaccine] research and political and economic policy, when he asserted that malaria eradication would benefit U.S. policy and finance. Similar sentiments are still being expressed, for example at the World Summit on Malaria in Amsterdam in 1992, Malaria is not just a troublesome tropical disease, it is an impediment to world development. The disease affects tourism and trade . . . [and] for the US, possibly the highest stake of all, was and is, military. (Turnbull 2000, pp 166 & 171)

In this way we can see that the inhibition of debate on issues pertaining to immunisation by evoking the dire consequences of reduced herd immunity and fear of epidemics may have significant social, political and economic implications.

The force with which the medical profession defends the preserve of immunisation arises in part from the perception that immunisation is the only tangible means to prevent infection, but also because immunisation is the epitome of medical technology. This view of "vaccines as magic bullets" (Dew 1999, p 381) arises because

> Medical science is a traditional natural science. It attempts to isolate distinct and identifiable diseases which are causally produced by some underlying patho-physiological condition which can be isolated, verified and monitored. . . It works most comfortably where there is a biochemical and/or structural defect that provides a simple key to understanding the disease being studied. It therefore tries to find such an entity or a surveyable and fairly small set of such entities for every disease. But the search may fail for a number of reasons . . . (Gillett 1994, p 1127)

In terms of immunisation, the reductive perspective of medical science is comfortable with the construct that there exists a discrete pathogen causing the disease, and administration of a vaccine provides safe pre-exposure and generates a memory response as protection. This is a clear cause and effect relationship. It creates a sense of order and predictability, it is statistically analysable. Unfortunately it bears little resemblance to the rich complexity of reality, and the

> . . . political over-reliance on [immunisation] as a source of disease prevention deflects health workers (and dependent parents) from utilizing other sources of legitimate knowledge about risk to infection. (Pilgrim & Rogers 1995, p 67)

Scientific literature itself reveals that epidemics of disease (including non-infectious conditions such as cardiovascular disease and cancer) arise from a complex interplay of factors that often defy a simple cause and effect explanation. Whether an individual is infected by an infectious disease such as measles is determined by the virulence of the particular strain of pathogen, the age, sex, number of siblings, race, stress levels, self-esteem and health of the host, the means of transmission, the time of year, annual agricultural cycles, socio-economic factors affecting the family, the community and the nation (see for example Aaby 1992; Aaby, Andersen & Knusden 1996; Aaby, Burstrom & Mutie 1992; Aaby & Lamb 1991; Aaby et al

1995; Desgrees du Lou, Pison & Aaby 1988; Guyer & McBean 1981; Karasek & Theorell 1990; Kiecolt-Glasser, Toovey & McDonald 1995; Krieger et al 1993; Paule et al 1979; Pison & Bonneuil 1988). It also matters whether the individual has been immunised, at what age, with which brand, what titre, the storage and transport conditions to which the vaccine had been subjected, how deeply the vaccine was injected, how the individual's immune system responded (see for example Aaby 1995; Herceg, Passaris & Mead 1994; Yaeger et al 1977). Whether a few cases of a disease develop into an epidemic depends upon all these factors in each individual that comes into contact with the pathogen, and the general physical, emotional and economic state of the whole community. It can also depend upon climatic factors. For example the best predictor of outbreaks of cholera in India is an unusally warm ocean current where the cholera pathogen breeds in the plankton blooms (Colwell 1996; Lipp, Huq & Colwell 2002; Tamplin et al 1990).

It is a matter of concern, therefore, that:

> While a considerable body of research supports the importance of a variety of "determinants of health" . . . almost no account is taken of such variables in the formation of health (care) policy. That policy is, by contrast, acutely sensitive to even the possibility that some new drug or piece of equipment or diagnostic procedure [or vaccine] may contribute to health. (Segal 1997, p 222)

The research on determinants of health suggest that the best defence against epidemics of diseases for which an effective vaccine exists, is immunisation used in conjunction with a holistic approach to public health. However, it should be recognised that immunisation is not the only, or necessarily the primary, protective factor in this complex equation. There are also many diseases for which vaccines do not exist. Immunisation does not, therefore, hold any privileged preserve that provides it with immunity from public debates over its relative value in any given situation.

14.5 ETHICAL ISSUES AND VALUES IN PUBLIC HEALTH

> When values are explicit, they may be openly debated but rhetoric uses metaphor to smuggle values into discourse that proclaims itself rational, even-handed and value-free. (Kirmayer 1988, p 57)

This comment is particularly pertinent to the scientific and policy literature relating to immunisation. The underlying values of ethical debates over informed consent, coercion and its justification by the utilitarian argument will be examined here.

14.5.1 COMPULSORY IMMUNISATION

Immunisation is the focus of contradictory policies. On the one hand informed consent is required for the procedure, and on the other hand it is either mandatory (as in the USA) or heavily advocated. Further complications are added to this situation by the existence, particularly in some industrialised nations such as Australia and the United Kingdom, of financial incentives for medical pracitioners to immunise. This is seen to compromise their capacity to provide impartial and balanced information to consumers (Nicholson 1996).

In the USA, completion of the childhood immunisation schedule is a compulsory requirement for school entry. The only variation between the states is the degree of difficulty experienced in obtaining exemptions on medical, religious or conscientious grounds. Some states use extremely coercive tactics, including removing children from their families and making children wards of the state to ensure maximum compliance (Anonymous 1991).

> When my child was 2 months old, I took her in for a well baby visit. . . I stood there in the Pediatrician's office and told Sophie's doctor that I only wanted to have 1 vaccine for the day. I explained that I was in no rush to flood her body with vaccines and I was concerned for her safety.
>
> Her doctor suddenly got very nasty with me.
> "Well the state of New Jersey has very specific recommendations and rules for Vaccinations you know. This is here to help her!"
> I calmly told her that I only wanted one vaccine for the day or I would leave.

> "This is mandated by the state", she snipped "If you don't have these shots, I am well within my rights to call DYFS for medical neglect."
> I was terrified, I was a new Mom with a tiny baby. Here I was being forced into shots and being threatened with Child protective services.
> (Anonymous 2003b, p 1)

> Ben worsened with the second hepatitis B immunization at 4 weeks. It was at this moment that I realized he'd been given the shot at birth [it appeared in his medical records from the hospital, but they had not known or given consent for it] and that this may be causing his problems. At two months I asked Ben's pediatrician to postpone his immunizations. I asked only for a delay so that Ben could continue recuperating. I knew that accepted pediatric practice dictates that a sick child should not be immunized. The doctor refused my request. When I persisted, he told me we could either immunize Ben on schedule, which we had to do because it was law. Or we could call DSS. With this threat, Ben was immunized. All of his symptoms worsened. [Ben is autistic and has grand-mal seizures].
> (Converse 2003, pp1-2)

In Australia and New Zealand, rather paradoxically, immunisation *choice* is mandatory (Dare 1998). Upon entry to child care or school, parents must provide a statement of the immunisation status of the child. They must either provide a certificate of proof of immunisation, or a statutory declaration that the child has not been immunised. In the event of an outbreak of a vaccine preventable disease an unimmunised child must be removed from school or care for the duration of the outbreak.

In recent years the United Kingdom in 1994 (Nicholson 1996), Australia in 1998 (Woolridge 1998), and New Zealand in 1997 (Dew 1999) have all run large measles immunisation campaigns based upon a mathematical model that indicated a measles epidemic was likely to occur in the near future

> . . . and which turns out not to have been validated using statistically reliable data. (Nicholson 1996, p 4)

In the United Kingdom it was known that “Senior government doctors had wanted for several years to run a measles vaccination campaign” (Nicholson 1996, p 4). Information provided by the Health Department

> . . . suggested that side effects to the vaccine were rare, mild, and transient, while measles itself was a devastating killer and cause of long term morbidity. Any questioning of that information resulted in endless repetition of how the campaign would stop an epidemic. (Nicholson 1996, p 4)

Immunisation was conducted through the schools, and parents were not present. This resulted in many children receiving the vaccine despite their parents having refused consent. It was also later discovered that the incorrect dosage had been administered (Nicholson 1996). The campaign resulted in legal action over a proportion of serious adverse events (Dyer 1994). Despite this the government declared it a success, and on this basis Canada, New Zealand and Australia followed suit.

The results of this campaign, and the treatment of Wakefield (see Section 14.4) have led to medical practitioners expressing unease with their role as immunisation providers:

> I have been increasingly uncomfortable when giving the combined mumps, measles, and rubella (MMR) vaccine. . . I find it difficult to be certain that the vaccine is as safe as the authorities say that it is. Somehow, the more strident the experts become, the less believable I seem to find them. . .The partial use of evidence that is apparent within official pronouncements is echoed by other experts. . . I am not alone in my concern, and possible confusion . . . a recent survey of health workers in north Wales [showed] only 45% of the professionals agreed completely with the policy of giving the second dose of the MMR vaccine. . . It is not easy to question authority these days . . . Perhaps keeping my head down and not even talking about these issues would be the easiest option. (Heller 2001, p 838-39)

In the other nations various persuasive techniques were employed to ensure maximum compliance with the immunisation campaigns. These included selective

use of the media, conducting immunisation sessions at schools, polling booths and McDonalds fast food outlets, and in one area in New Zealand with a high Maori and Pacific Islander population, a bus patrolled the streets with loud hailers, and a door-to-door campaign was conducted urging people to immunise (Dew 1999). Interestingly, in New Zealand the incidence of measles was higher in Pacific Islanders. This was explained only in terms of (unverified) low levels of immunisation. Socio-economic or genetic factors were “not given any real credence in media reports” (Dew 1999, p 386).

So despite nations such as Great Britain, Australia and New Zealand having a policy of mandatory choice, there is still a significant degree of pressure to comply with both the general childhood immunisation schedule, and with intermittent campaigns. Depending upon the perspective taken on immunisation, this may either be seen as positive health promotion or coercion.

An interesting aspect of these government policies is the association of immunisation with the education system. In the USA a completed immunisation schedule is compulsory for school entry. This means an unimmunised child whose parents are unable to obtain an exemption may be excluded from the education system. The states of the USA vary considerably in their requirements for exemption, and some families have moved to obtain the exemptions they require (National Vaccine Information Centre, USA 2003).

In Australia and New Zealand declaration of immunisation status is compulsory at school entry. An unimmunised child is required to be removed from school in the event of an outbreak of a vaccine preventable disease. This means that if the parents have chosen not to have their child immunised, the child may be

discriminated against by missing educational opportunities, and/or being singled out in class, and the parents may be discriminated against financially by having to find child care or take time from work for the duration of the outbreak. The reason given for the exclusion is that it is to protect the unimmunised child from the epidemic. This is despite the fact that vaccinated children may not have sero-converted, or their protection may have waned (Galil 2002). Targeted immunisation campaigns are often carried out at school, in the absence of parents. This has led to children being immunised without parental consent, or even after parental refusal (see for example Nicholson 1996; OHCC 1998).

This linking of immunisation with school attendance has been seen as an extension of medical hegemony into the education sector, and using the right of access to education to ensure conformity (Dew 1999). Similarly there have also been moves to link immunisation with receipt of government benefits. In Australia a $200 Maternity Immunisation Allowance has been payable when the child is 18 months old and fully immunised. This is also payable if parents provide a statutory declaration of conscientious or medical exemption. It was advertised as “tax-free money to encourage parents to immunise their children” (Centrelink 1997). In New Zealand a survey regarding a proposed Code of Social Responsibility sought public opinion on linking immunisation with receipt of income support for parents.

> . . . it can be seen that this Code is designed to impel those who have the least ability to resist, that is, those on welfare, to have their children immunized. . . Parents of children brain-damaged following vaccination have responded to such proposals by asking who is responsible for their own tragic outcomes. (Carter 1998 in Dew 1999)

This is despite evidence that it is the children in these poorer socio-economic groups who are less likely to mount an adequate response to the vaccines because of all the previously outlined attendant factors.

It is therefore evident that even nations which apparently eschew legal compulsion to immunise implement many other means of coercion. Linking immunisation compliance with access to other fundamental social services such as education and welfare, provision of which are covered by the United Nations Charter on the Rights of the Child and the Declaration of Human Rights is an issue of great concern (WHO 2003). This is because the values and compulsion are, as Kirmayer (1988) would put it "smuggled in".

14.5.2 FINANCIAL INCENTIVES FOR MEDICAL PRACTITONERS

In Australia, since 1998, medical practitioners have received, from the government, a financial incentives package made up of three components: the consultation fee, a Service Incentive Payment payable on receipt of notification of the completed schedule to the Australian Childhood Immunisation Register (ACIR), and an Outcomes Bonus Payment provided three monthly in arrears and based on the percentage of children in that practice who have been fully immunised. This last payment is tiered for percentages of 70%, 80% and 90% (Alzois 1998).

Very similar financial incentives are also in place in the United Kingdom. Criticisms have been levelled at both systems, but particularly the system in the United Kingdom, because these medical practitioners have small, clearly defined populations in their practices and on average only thirty children become eligible to complete their immunisation schedule each year. This means that

> . . . refusal of immunisation by just three or four families carries considerable financial implications, resulting not only in coercion at the local level, but also in families being told to find a different GP. (Nicholson 1996)

A medical practitioner described the incentive scheme as a significant reason to maintain immunisation in the face of personal doubts.

> Missing these targets would have serious consequences for the financial stability of the practice, and there is considerable pressure on members of the team to ensure that children are immunised with every recommended vaccine. (Heller 2001, p 838)

Government policy in the United Kingdom appears to be following the USA model towards compulsion, for example

> In May 1995, armed police and social workers arrived at a house where a baby girl had just been born to take her away to be immunized against hepatitis B. Her parents were happy for her to have immunoglobulin, but had once expressed serious doubts about vaccination because it caused a severe skin rash in her elder brother. No further effort was made to discuss the problem with them. Instead, within hours of her birth, a public health doctor arranged for a High Court judge to make her a ward of court and to order her immunization without the parents having any chance to be heard. Nine months later, the High Court still has not heard them or their medical experts, yet the wardship continues in case the child needs an unprecedented fourth injection. Since governmental ministers at the Northern Ireland Office know about the case and have chosen not to intervene, one must assume that the U.K. government is now content to move toward quite extreme forms of compulsion in vaccination. (Nicholson 1996, p 4)

However the prevailing ethos in Europe is towards voluntary immunisation. In the USA where it is compulsory, coverage rates are estimated to be between 83 and 95% (Dare 1998; Nicholson 1996). In European countries where immunisation is voluntary, coverage rates are comparable, for example 93% in the Netherlands, 92% in Sweden (Dare 1998) and 97% in Finland (Nicholson 1996). These figures provide no basis to support making immunisation compulsory, and yet this issue arises regularly on the agenda of English speaking industrialised nations such as Great Britain, Canada, Australia and New Zealand who are influenced by policy trends in the USA (Dare 1998; Nicholson 1996).

14.5.3 INFORMED CONSENT

This trend towards coercion sits very uneasily with a corresponding increase in emphasis on the need for informed consent for medical procedures including immunisation. In Australia between 1997 and 2000, the NHMRC rewrote the section in its Immunisation Handbook on consent to include the recommendations that:

> Extra information should be available if parents or the vaccinee request it. The vaccine provider should allow time for a discussion with the individual to ensure the issue of risk has been addressed. (NHMRC 2000a, p 14)

The emphasis on obtaining informed consent is based on "our respect for the autonomy, dignity, and self-determination of patients" (Bernat 2000, p 614) and that:

> Preservation, even enhancement, of patient autonomy is a central obligation of contemporary medical ethics for the very good reason that it is firmly rooted in the obligations we owe each other as human beings, endowed with intelligence . . . (Pellegrino 1984, p 83)

It also has the practical application of assisting in avoiding costly litigation in the light of an iatrogenic event. In the USA, all citizens hold a Constitutional right to refuse any medical therapies, including life-sustaining ones, even if they will die as a result. However, while parents or guardians acting on behalf of their children may have the theoretical right to refuse immunisation, in effect such choice is constrained by the consequences of such a decision. Even when the decision not to immunise the child is made, some state governments will override the wishes of the individual in certain instances (Anonymous 1991). On the other hand, little attention has been paid to the ethical and legal situation that would ensue if a child who is unimmunised because the parents claimed a philosophical exemption catches a vaccine preventable disease and suffers severe side-effects (for a general discussion on children's rights see Spenser 2000; Reckling 1994).

It has been argued that in the matter of preventative rather than curative medicine insufficient attention has been given to the issue of autonomy:

> The central, unavoidable dilemma is that effective preventive measures can benefit a whole society only if they limit autonomy and involve some coercion. The focal ethical question in preventive as opposed to curative medicine is to what extent, and under what circumstances, can personal autonomy be abridged to promote the health of the whole community? (Pellegrino 1984, p 84)

To be effective, the implementation of many preventive health measures such as water treatment, alcohol consumption limits for driving, restrictions on smoking etc involve a degree of compromise of personal autonomy. However, these measures differ in some important respects from immunisation.

Firstly the proof of causal links between the undesirable behaviour and adverse health outcomes in these examples is fairly straight forward. There is little social dispute of the link between water pollution and contamination and associated negative health results, in fact there are community lobby groups who argue for tighter controls on water pollution and urge wider provision of safe water facilities (ESW 2002). The connection between increased blood alcohol levels and reduced driving performance, and smoking and passive smoking and lung diseases has wide scientific and lay acceptance. Secondly these are all behaviours that involve adults taking responsibility for their own behaviour, and they are behaviours which generally have minimal negative outcomes for the individual who complies with the regulation. Restricting alcohol and cigarette intake or disposing of chemicals in a manner that reduces pollution do not generally carry the risk of immediate or long-term adverse health outcomes.

Immunisation, however, involves an invasive medical procedure applied to ‘healthy’ children. It is known to carry the risk of both immediate and possibly long-term negative health outcomes, its benefits are less guaranteed (the immunisation may

not seroconvert, or protection may wane) and less directly obvious. Pellegrino stipulates that:

> Where the value of a preventive measure is only speculative, coercive measures cannot be morally justified. The obligation rests instead on those who suggest a causal connection between some life-style and a given disease entity. Those who propose new preventive measures for wide application are under obligation to report their data honestly and with scientific rigor. Uncertainties should be spelled out lest they lead to unnecessary expenditures, and changes in people's lives or raise false expectations. (1984, p 90)

While few in the medical profession would see the value of immunisation as 'speculative', even evaluating it as an established preventive measure, it fails on each of these counts. Immunisation may have been a contributory factor to the decline in some infectious diseases, but in many cases what has been presented as a clear causal link has been influenced by wider socio-economic factors that are not given due recognition. Data pertaining to immunisation safety and efficacy has not always complied with high standards of scientific rigor. There have been significant problems with methodology, measurement parameters and vested interests. Uncertainties, whilst openly discussed in the literature of the scientific community, have tended to be excluded from information presented in the public domain. Immunisations have sometimes been recommended for general public use without the support of adequate data on safety and efficacy. On all these counts immunisation fails the requirements whereby Pellegrino holds that coercion would be morally justified.

A further issue of concern is that immunisation has been coercively promoted to the neglect of other fundamental health requirements.

> In a day of high level social, environmental and medical technology, [in the USA] we continue to find over five million children living in homes with leaky roofs, nearly 1 ½ million without a piped water supply and nearly 22 million without the availability of public sewerage . . . likely to be associated with rural poverty. These circumstances simply confirm that all children are not equal in what they have, need, want or deserve. That inequality persists is evident. (Pellegrino 1984, p 186-87)

Similar situations exist in the United Kingdom and Australia (ABS 2003; Office for National Statistics (UK) 2003).

There is no serious dispute that the funds exist to address this situation. What is lacking is the motivation to constructively address the situation. For example:

> It is obvious that current governmental policies place a high priority on maintaining defence resources and are aimed at reducing support for child health and welfare resources. Poor children, despite their greater needs, are at particular risk of losing economic benefits as well as health screening and treatment programs . . . (Pellegrino 1984, p 187)

This is probably even more the case in the current political climate than it was in 1984 when this comment was made. It is possible to view immunisation as playing a similar role within industrialised nations as it plays in their relationships with developing countries, that it provides a medically and technologically approved appearance that health issues are being constructively addressed when more serious, fundamental and difficult-to-address health issues related to socio-economic inequalities are quietly side-lined.

14.5.4 THE UTILITARIAN ARGUMENT

The primary philosophical argument used to justify compulsion to immunise is provided by the utilitarian argument, which is most simply put as ‘the greatest good for the greatest number’ (see for example Sykes 1976). For immunisation:

> The main purpose of preventive medicine and the measures recommended by its theorists to public health authorities is, obviously, the prevention of diseases. Sometimes, however, proper preventive measures cause disease [or death] in the population as well as helping to avert them. . . . [This] raises ethical questions concerning the fate of those victimised in the process. . . According to a rough-and-ready utilitarian calculation, such measures should be taken. (Håyry & Håyry 1989, p 43)

Articles on this issue (see for example Håyry & Håyry 1989; Unger 1992) discuss standard philosophical objections and their counter arguments, which can be summarised, in a very simplified form, as follows:

> The protection of the community as a whole from disease justifies the illness or death of a few.
> Coercion is an evil in itself, an evil so great that simple utilitarian calculations cannot justify its use in any circumstances.
> The objectors to coercion are risking severe harm to their own children and to other people by not having their children vaccinated, so to prevent this some (usually very mild) coercive measures are justified.
>
> There are likely to be some deaths as a result of the vaccine. There is no way to justify the direct killing of innocent people by referring to the benefits to others.
>
> These deaths are an unfortunate indirect result, not a result of direct intent, therefore they are morally permissible. Those who are protected by the immunisation campaign have the right to be protected.(from Håyry & Håyry 1989; Unger 1992)

The customary conclusion of the utilitarian argument, as summarised by Håyry & Håyry is:

> It can be admitted that it is a great evil indeed to have to sacrifice human lives in a vaccination programme. But it must be remembered that the many people who would die in case not enough education and information were given have a right to live, too, and neither should they be sacrificed to save the victims of the vaccine. There are rights, evils and sacrifices on both sides, and thinking about them alone will not solve the problem of what should be done. As something, however, will be done . . . and as choices must be made, the rough-and-ready utilitarian calculation is after all the best device we have to justify our decision. And this decision . . . is clearly in favour of vaccinating. (1989, p 50)

Depending on the view taken of utilitarian thinking, as far as a theoretical philosophical argument is concerned, there are no great problems with this conclusion. The problems with the utilitarian argument in defence of immunisation occur when one examines its application in the real world. The two most significant problems here are the narrow focus of the argument, and its inconsistent application as influenced by vested interests and government policy.

Firstly, whenever the utilitarian argument is used to justify immunisation programs, it is discussed in isolation. It is not accompanied by any mention of broader public health issues or other potential approaches to minimising infectious disease. The same utilitarian argument used in a broader context brings a different result. We are seeking the greatest good of the greatest number and we have a variety of options.

One option is to conduct a large immunisation campaign which will provide most (but not all) recipients with protection from a limited number of specific infectious diseases. However, this protection will vary significantly between the individuals who receive it, and it will wane over time. The immunisation campaign will also result in a proportion of recipients experiencing adverse reactions of varying degrees of intensity from a few hours of discomfort to long-term adverse health outcomes of varying severity, and in a few cases even death.

Another option is to spend the same amount of money to improve the population's access to safe water and adequate sewerage. This will provide protection from a greater number of diseases, some for which vaccines exist and some for which they don't. This will bring about a permanent improvement in health for the entire community, although some may benefit directly more than others, with minimal adverse health outcomes or deaths.

Even at this simplistic level, and there are many more public health and general economic policies which could be added into the equation, the same utilitarian argument can be used to show that immunisation is not necessarily the most rational, cost effective or beneficient option.

The second point to be made is that there is evidence that the utilitarian argument has been used selectively to suit health department policy. For example the *Measles Information Booklet* released for the measles immunisation campaign in Australia in 1998 carried the slogan:

> We can protect our children from the threat of measles – But only if we work together.

The consent form also stated in bold print:

> By protecting your child from measles you are helping to protect the community from an epidemic.

However the case of Hepatitis B in the United Kingdom provides an example of different values directing policy. In this case, the high cost of the vaccine and maintaining the reputations of senior health workers were the significant determining factors in policy development, until the potential cost of ligitation from failing to immunise outweighed these factos in significance.

As Hepatitis B is spread by contact with body fluids, it is a disease that is identified with homosexuals and drug users. It also became a significant issue for health care workers on two counts. Non-infected health care workers could become infected from contact with their patients, and health care workers who were infected could pass the disease on to non-infected patients.

An initial consideration in the case of Hepatitis B policy in the UK, was that the vaccine was considerably more expensive than many of the traditional paediatric ones. In the 1980's the cost of a course of vaccine was UK£60. However a similar vaccine was available from an Asian manufacturer for US$1 a course. As one article concludes:

> Further study is required, of World Health Organization input and the arrangements by which pharmaceutical companies are licensed to manufacture and sell their vaccines in different countries, in order to explain

> this remarkable price differential which has been maintained over many years. (Stanton 1994, p 432)

Eventually a cheaper vaccine was developed, and although the cost of the vaccine was a consideration,

> . . . the pharmaceutical companies which manufactured and distributed the vaccine conducted a persistent campaign to promote their product (Stanton 1994, p 444),

it was other issues that drove the debate over policy. While the epidemiology or potency of a disease would seem a logical determinant of policy, it is not necessarily the main determinant. Rather it is "changing social relations of power in the medical and health care arenas" (Stanton 1994, p 444) and "the reluctance of health professionals to encourage fully informed public debate" (Stanton 1994, p 433)

With previous infectious diseases for which a vaccine was available, the use of the utilitarian argument to justify mass immunisation campaigns had been customary, but this did not happen with Hepatitis B. The history of policy for Hepatitis B immunisation amongst health care workers in the UK is complex, and showed gradual shifts over time. However a distinctive feature that emerges is that the major risk was defined as patients infecting health care workers, with the contrary situation of a health care worker infecting a patient regarded as "extremely rare" despite a number of incidents where patients were infected with Hepatitis B by carrier surgeons (Stanton 1994). A protective policy of screening health care workers to determine carriers was not implemented because:

> . . . there might be too many, and especially too many among the higher status groups such as surgeons . . . In the balance of individual rights versus public health interests, at this stage there seemed good reason to favour individual rights. (Stanton 1994, p 445)

It is of particular note that even after an affordable vaccine became available and

> . . . it was in both the individual's and the public health interest to initiate widespread screening and vaccination. But the centrality of health workers . . . kept individual rights. . . at the forefront of the agenda. (Stanton 1994, p 445)

It is also of note that this consideration of the rights of the individual over the health and safety of the community came at a time when the UK Department of Health was going through a period of "increasingly stringent cost-cutting" (Stanton 1994, p 446) and therefore reluctant to pay for the vaccine. This changed after the advent of AIDS in the mid-1980's, as this highlighted many issues of relevance to Hepatitis B such as needle use for intravenous drug users, and extended the range of reference past health workers in an atmosphere that made it harder for the Department of Health to maintain its "weak vaccine policy" (Stanton 1994, p 446). In addition there were changes to the law affecting the liability of the Department of Health as an employer, leading to potentially expensive litigation costs if it failed to immunise its employees. Also at an international level there was a call to advocate wider immunisation, and now in the United Kingdom, as well as in many other countries including Australia, universal childhood immunisation against Hepatitis B is now advocated at birth.

There are still variations in policy between industrialised nations on Hepatitis B immunisation. In 1998 Canada decided to immunise 9-13 year olds through the school system prior to adolescence when they are perceived to be at risk from contracting the virus through sexual contacts. Universal infant immunisation was discounted because of the low prevalence (less than 3%) of the virus among young children with no known risk factors (Scheifele 1998). At the same time the USA implemented universal childhood immunisation with Hepatitis B vaccine on the basis that:

> Acute hepatitis B infections are usually asymptomatic in children, although infants and children 5 years of age or younger have the greatest risk of

> developing chronic hepatitis B and, later in life, its serious sequelae. (Arnot 1998, p S27)

Another factor in this consideration is that children are regarded as a “captive population” (Takayama 1999, p 325).

From this discussion on hepatitis B vaccine it can be seen that professed values behind public immunisation, that is the protection of the community from infectious disease, are actually influenced by many factors. These include political and financial issues, and vary over time and between nations. Once again, although the values are presented as explicit, and eloquently supported by the utilitarian argument, a variety of political and financial issues are actually the primary influence. These agendas have been “smuggled” into discourse that “proclaims itself rational, even-handed and value-free” (Kirmayer 1988, p 57).

14.6 THE POLITICS OF COMPULSORY IMMUNISATION

One explanation that has been proferred for this is in the context of the rise of the neo-liberal state. The state is unable to guarantee the health of the population, but to appear to do so it seeks “quantifiable variables which become a surrogate for health” (Osborne 1997, p 185). In this context immunisation levels become important indicators of the success of the health system, “no matter what relationship this has to actual levels of health or protection from disease” (Dew 1999, p 392). In the drive to deregulate the economy and encourage privatisation including in the health sector, the government must find a way to make it appear as though services are still being provided. Typically this is through more regulation and more policing of those who provide these services. This may offer some insight into why it is the USA that has the most stringent laws enforcing compulsory immunisation.

> The state most committed to freeing market forces is also the most committed to ensuring surrogate health targets are met. Any indications that

> vaccinations may actually increase ill-health, due to such things as adverse reactions, delaying disease to a later age and losing protection for infants, are ignored or belittled. It is in the interests of health officials to find as few problems as possible with their policies, and mono-causal explanations of events used in vaccination policies reinforce efforts to acquire more resources. (Dew 1999, p 392)

Tight monitoring of immunisation levels serve two purposes. They demonstrate the success of state health interventions during a period of economic deregulation, and they provide a means of accumulating population data. The linking of immunisation with school entry has provided a means to correlate information on health and education. Further to this, it has been proposed that the notion of 'informed choice' has been used as a screen for the degree of coercion and indoctrination, with penalties such as withdrawal of rights to welfare and education if an individual makes the wrong 'informed choice'. This is seen as a transition of health from a right of citizenship to a duty of citizenship (Lupton 1995; Osborne 1997). This correlates with the perspective discussed in Chapter 13 that improving health will alleviate poverty by increasing the individual's capacity for productivity, and it was shown in that Chapter that the causality was neither that way around, nor that simple.

14.7 THE DEONTOLOGICAL POSITION

Contrary to the Utilitarian Argument, the Deontological Position is based on the principles of universalisability of moral rules and respect for autonomy. Humans are given a special status as "moral beings" and value is placed upon recognising and respecting the dignity of the individual. It is not morally permissible to use others for one's own ends. From this moral perspective individual rights are not subordinated to the good of the majority. It is this perspective that underlies the United Nations Declaration of Human Rights (1948), and the Declaration of Alma-Ata (WHO 1978).

The Declaration of Alma-Ata (WHO 1978) argues that health, as a state of complete physical, mental and social wellbeing, is a fundamental human right. Primary health care should be made universally accessible to individuals and families . . . “in a spirit of self-reliance and self-determination” (WHO 1978, sect. IV). It is not framed in a manner that would support the immunisation of individuals, without their consent, for the sake of the community as a whole.

The deontological position provides a philosophical basis for the development of Public Health Care Policy and its practical implementation that is in accordance with the findings on individual and national health outcomes that were outlined in Chapters 11 & 12. In comparisons both within and between nations, the greater the degree of autonomy, security and community support experienced by individuals, the more positive were their long-term health outcomes. This is compatible with a policy of well informed but voluntary, rather that mandatory, immunisations.

There has been an historical reliance upon the Utilitarian Argument to support mandatory immunisation and mass immunisation programmes. However, the Utilitarian Argument sits uneasily with the philosophical basis for primary health care on both an international and national level. It is also at odds with the increasing emphasis on obtaining informed consent for medical procedures. A Deontological Position which focuses on respecting the autonomy and rights of the individual is more in line with Public Health Care policy and positive long-term health outcomes.

14.8 CONCLUSION

This Chapter has demonstrated that the policies and information presented to the public regarding immunisation are portrayed, by governments and medical professionals, as rationally based upon sound scientific evidence. The situation is,

however, influenced by a range of political and financial issues. Information about reactions to immunisation is collected and controlled by the scientific community, in various ways, to remain within limited and pre-determined parameters. Contrary evidence and views are ignored or denied by the scientific community, governments and medical professionals, in general. Professed utilitarian values are justifications for agendas of financial policy, political power and the need for the government to be seen to be proactive in public health, despite poor performance in many key health areas. However, these utilitarian values are at odds with the more deontological stance that underlies the development and implementation of public health care policy at both international and national levels, and the growing emphasis on informed consent.

These practices persist despite the increasing access by the public to the same scientific literature as has previously been the province of medical professionals and a growing public awareness of the contradictory nature of this literature. Recent moves, in some nations, towards voluntary immunisation policies and increased consumer reporting of adverse events, indicate that the increase in public awareness of the debates around immunisation issues are beginning to exert some influence on the development of public policy that respects individual rights.

CHAPTER 15

THE AUSTRALIAN SITUATION

15.1 IMMUNISATION IN AUSTRALIA

The situation regarding immunisation in Australia is comparable to that in the other English-speaking industrialised nations such as the United Kingdom, USA, Canada and New Zealand. The USA is the only nation where immunisation is legislated to be compulsory (with state-based variations in allowable exemptions), as discussed in Chapter 14. In Australia, as in the other nations, immunisation is highly advocated but remains voluntary. However, immunisation *choice* is mandatory. A statement of immunisation status must be provided upon the entry of a child into childcare or school, this means that the parents must effectively choose whether to immunise or obtain a statutory declaration or medical certificate claiming exemption (Dare 1998). In the event of an outbreak of disease, an unimmunised child may be required to stay home until the end of the outbreak. This measure is deemed to be for the child's protection. In the State of Tasmania, childcare centres and schools are required, by law, as stated in the *Public Health Act 1997*, to keep copies of the child's immunisation status (Jacobs 1997; Parliament of Tasmania 1997). Similar provisions apply in other states and territories.

Exemption on the grounds of religious or philosophical objection requires a simple statutory declaration of that position. Exemption on medical grounds requires a statement from a medical practitioner. Provision of either of these exemptions entitles parents to receipt of immunisation-linked benefits such as the Maternity Immunisation Allowance, which is a lump sum payment made upon completion of the 18 month childhood immunisation schedule.

This policy maintains a balance between community obligation and individual rights. Immunisation coverage is over 90% in industrialised nations where it is voluntary (see Section 14.5.2) and Australia's childhood immunisation rates are well over 90% under this arrangement (GPPAC 2003). Given the broader community and personal health value of preserving patient autonomy (Pellegrino 1984) the Australian scheme appears optimal and a case for further compulsion seems difficult to sustain.

15.2 FINANCIAL INCENTIVE SCHEMES

In Australia, medical practitioners obtain funding from a variety of incentive schemes that cover a wide range of health issues including asthma, diabetes, mental health and several preventative health measures including immunisation. In 1998 the federal government introduced a financial incentive scheme for immunisation that is similar to that of the United Kingdom. As outlined in Section 14.5.2 it is made up of a consultation fee, a Service Incentive Payment for notification to the ACIR, and an Outcomes Bonus Payment based on the percentage of children in that practice who have been fully immunised (Alzois 1998).

The Service Incentive Payment (SIP), which is paid upon notification of immunisation completed to each of the six age requirements (ie 2, 4, 6, 12, & 18

months and 4-5 years) to the Australian Childhood Immunisation Register (ACIR) was instituted to address problems with notification of immunisation. The ACIR sends automatic reminder notices to parents when immunisations are overdue. Failure to report by medical practitioners had resulted in unnecessary reminders being sent. It also meant that immunisation statistics were underreported and thus the ACIR was unable to fulfil one of its primary functions, which was to monitor immunisation patterns and provide a tool for policy formation and planning (McIntyre et al 1998). Immunisation coverage as recorded by the ACIR has increased from 73% in 1998 when the SIP started, to over 90% in 2001 (GPPAC 2002). As the immunisation figures collected by the Australian Bureau of Statistics do not show the same variation (ABS 2003), and as a study in 1996 showed under reporting to the ACIR of 27%, the majority of this increase represents increased reporting by medical practitioners, attesting to the effectiveness of the incentive payment (McIntyre et al 1998).

In the United Kingdom, medical practitioners have a set geographical area to service. This has caused problems with the immunisation bonus scheme as there are incidents of medical practitioners refusing to service non-immunisers who jeopardise their receipt of the bonus payment (Nicholson 1998). In devising the Australian immunisation incentive scheme, it was recognised that the population is mobile, and that a significant proportion of children will visit more than one medical practice during their first seven years, or be immunised outside medical practices, for example at clinics run by local councils. To allow for this, the Outcomes Bonus Payment is based on a proportion of whole patient equivalent values (WPEs) calculated for each child using data from the medical practice, Medicare and ACIR. In this manner each practice receives a proportional bonus payment for the services provided (Hornsby Ku-ring-gai Ryde Division of General Practice 2003). This does not address the issue of medical practitioners pressuring patients into

immunisation to ensure they receive financial benefits, but it does perhaps mean that they are more conscious of providing quality service to prevent patients obtaining services elsewhere and thus reducing their WPEs.

15.3 REPORTING OF ADVERSE EVENTS

To their credit, Australian authorities have broadened their parameters for acceptance of reports of adverse events. In 1997 ADRAC required reports of anaphylaxis, shock and hypotonic/hyporesponsive episodes within 48 hours, and specified six more conditions (plus "other") within 30 days. The Immunisation Handbook issued in 2000 presents a more comprehensive discussion of the issue and lists 30 conditions (plus "other") to be reported. It also specifies that

> No time limit has been set, as some adverse events related to vaccination could occur many years later. . . Medical practitioners or other health professionals are free to report any adverse events that concern them, but do not fit into any of the above categories. (NHMRC 2000a, pp 22-23)

This attitude is far more conducive to encouraging reports of a wider range of information.

However, variation exists in the reporting requirements between the states. In NSW, Northern Territory, Queensland & Western Australia, immunisation providers are required to notify the relevant State or Territory Health Department, which will then notify ADRAC. In South Australia and the Australian Capital Territory reactions are not notifiable, but providers may voluntarily inform the relevant Health Department. In Victoria and Tasmania providers are requested to notify ADRAC directly (NHMRC 2000a). This variation in requirements where it is mandatory for some states but not for others, means that many adverse events are unlikely to be reported. It means that data on contaminated lots of vaccine cannot be adequately

assessed on a national level. It also means that national patterns, or state variations in reaction patterns cannot be adequately assessed. This situation needs to be addressed with a consistent nationwide requirement on reporting of adverse events.

15.4 THE ALTERNATIVE CONSUMERS' PERSPECTIVE

Australia has an active group that provides an alternative perspective on immunisation for consumers in the area of immunisation. The Australian Vaccination Network has a website (AVN 2003) and has produced a book (AVN 1998) and a video (Taycare 1998). They provide a range of scientific information and alternative health viewpoints on immunisation to interested consumers. They offer a support service for consumers who have experienced a traumatic adverse reaction, and they lobby politicians to ensure that choice over immunisation is preserved. Their literature carries stories of consumer dissatisfaction with the attitude and performance of medical practitioners. These are comparable with the consumer reports from similar groups in other nations, but it appears that Australia has been generally free of the more extreme forms of coercion evidenced in the USA and to a lesser extent in the United Kingdom (see Section 14.5.2). The most common Australian complaints about medical practitioners focus around lack of respect for parents with alternative health perspectives, arrogant or unsympathetic attitudes, providing immunisation without adequate information or follow through support regarding adverse reactions, failing to record batch numbers or reactions on medical records and refusing to acknowledge or report adverse reactions (AVN 1998; see Section 14.3.2.2).

Consumers who are unhappy with their treatment are able to report their concerns to the Health Complaints Commission in the relevant state or territory. As these

Commissions are State-based their approaches may vary. Members of the Australian Vaccination Network will assist with preparing the complaints on request.

15.5 VACCINE SUPPLY

Australia has one local vaccine manufacturing plant, the Commonwealth Serum Laboratories (CSL). It is registered by WHO as a United Nations qualified producer of vaccines for diphtheria/tetanus (DT), diphtheria/tetanus/pertussis (whole cell) (DTP) and tetanus toxoid (TT) (WHO 2002b). It supplies these vaccines to the Australian market.

For each of the main paediatric vaccines Australia has several licensed options from a range of suppliers in addition to CSL. This provides security in the case of emergency requirements, or disruption of production at a particular plant.

The vaccine manufacturing companies maintain small amounts of reserve stock, and the CSL maintains a small reserve stock of all products it markets here in Australia. State Health Departments also maintain reserve stocks. These reserve stocks, and the fact that two or more vaccines are licensed for use for each of the main paediatric immunisation requirements, mean that Australia's supply position is quite secure.

VACCINES CURRENTLY LICENSED FOR USE IN AUSTRALIA

Vaccine	Number of Licensed Vaccines	Vaccine Name	Producer
Hib	6	**Pedvax HIB (liquid or lyophilised)**	CSL/Merck Sharpe & Dohme (MSD)
		Comvax	
		HibTITER	Wyeth Lederle (WL)
		Hiberix	Smith Kline & Beecham (SKB)
		ActHib	Pasteur Merieux (PM)
DTP	3 acellular	**Infanrix**	SKB
		Infanrix-hep B	SKB
		Tripacel	CSL/PM Connaught
	1 whole cell	Triple Antigen	CSL
MMR	2	**MMRII**	CSL/MSD
		Priorix	SKB
OPV	1	**Polio Sabin (oral)**	SKB
IPV	1	IPOL (Inactivated)	CSL/PM
Hep B	5	**Energix B**	SKB
		HBVaxII	CSL/MSD
		Infanrix-hep B	SKB
		Comvax	CSL/MSD
		Twinrix - adult	SKB
		- junior	SKB

Vaccines in bold are those currently available for use (from NHMRC 2000a).

15.6 SERVICE PROVISION

In providing vaccines to the consumer the Australian market faces the same problems that are experienced to varying degrees in all nations. There are problems with cold-chain maintenance and the performance of immunisation providers.

In Australia the greatest problem with maintaining the cold-chain is ensuring that vaccines are not kept too cold, or even frozen during transport in hot climates (Eizenberg 1998; NHMRC 2000a, p 72; Svanberg & Platt 1998). There are also storage problems at a significant proportion of medical practices, with incorrect

refrigeration storage temperatures and locations and inadequate monitoring procedures (Herceg, Johns & Longbottom 1997; Martin, Nayada & Kempe 1998; Miles 1993).

Medical researchers express concerns about medical practitioners not adhering strictly enough to the NHMRC guidelines on when to immunise. The guidelines state that immunisation should be carried out except in the case of a major illness because:

> Major illness or high fever [over 38.5°C] might be confused with vaccine side effects and increase discomfort to the child. Therefore vaccination should be postponed for 2-3 days until the child is well. A return appointment for vaccination should be made at the time of referral. (NHMRC 2000a, p 41)

The only contraindications for DTP are encephalopathy within 7 days or severe allergic or anaphylactic reaction to a previous dose. “True contraindications to other vaccines are extremely rare” (p 41). These guidelines are comparable to those recommended world-wide by the WHO (2002c). However medical researchers find that some medical practitioners habitually defer immunisation if the child is mildly unwell, or split the schedule over two appointments and do not always offer opportunistic immunisations during appointments for other concerns (Kable & Harris 1997).

Although these matters of non-compliance with the NHMRC guidelines may be seen by the regulating bodies as issues to address in terms of ensuring that medical practitioners achieve maximum immunisation coverage, they are viewed very differently by the consumers. There is no evidence of consumer complaints over medical practitioners deferring immunisation of a slightly unwell child, or of splitting the schedule over two appointments. In fact these behaviours are seen as caring and considerate, and often made in response to consumer concerns for the child’s well-being (AVN 1998). There has been little research into the relative efficacy of splitting the administration of the schedule over two appointments, as

the emphasis has been placed on providing all scheduled vaccines at the one appointment to ensure provision and simplify record keeping (Herceg, Johns & Longbottom 1997; NHMRC 2000a). This discrepancy can be viewed as further evidence of the conflict between medical and government policy that seeks maximum community coverage, and the rights of the individual to ensure the best treatment for each child (Dare 1998; Dew 1999).

15.7 ABORIGINAL AND TORRES STRAIT ISLANDER HEALTH

15.7.1 GENERAL HEALTH CONCERNS

Aboriginals and Torres Strait Islanders comprise just under 2% of the total Australian population (Australian Bureau of Statistics 1997). Their health status is significantly poorer on all counts than that of the non-indigenous population, including that of recent migrants and refugees:

> Indigenous Australians suffer a higher burden of illness and die at a younger age than non-indigenous Australians, and this is true for almost every type of disease or condition for which information is available. (McLennan & Madden 1997, p 1)

Their life expectancy is still 15-20 years lower than for non-indigenous Australians, and the infant mortality rate is 2-4 times higher (Australian Bureau of Statistics 1997).

A multitude of historical, cultural and political factors have contributed to this situation. These include the invasion of their land by Europeans and Asians with no appreciation of their cultures, the destruction of their cultures by the alienation of land for settlement and the destruction of family and kinship systems by successive policies of assimilation and seizing of children in the ‘stolen generations’. Policies of assimilation were only discontinued in the early 1970’s, so many indigenous families are still dealing with the ongoing effects (Human Rights and Equal Opportunities Commission 1997).

The indigenous population was generally granted citizenship rights in Australia in 1967 (Aspin 1996) and with it came rights to equal wages and rights to welfare. As a result, many indigenous workers lost their low-paid rural work and were forced onto welfare (Aspin 1996). The resulting social, economic and health problems have been exacerbated by a piecemeal approach from all levels of government:

> With services and programs being delivered by Commonwealth, State, Territory and Local government agencies, there is no clear delineation, or agreement, about which level of government is ultimately responsible for ensuring there are continuing improvements in the health of Australia's Indigenous population. There appears to be little, if any, coordination between these diverse Commonwealth/State health programs, other environmental programs or programs provided through other agencies, in areas such as education and employment. (House of Representatives Standing Committee on Family and Community Affairs (HRSCFCA) 2000, p 1)

The *Health is Life: Report on the Inquiry into Indigenous Health* (HRSCFCA 2000) therefore recommends that "in the circumstances only the Commonwealth [the national government] can provide the necessary leadership and coordination" (p 1).

There is an appreciation that the causes of poor health and poverty are complex. The doctor in charge of a Victorian State Government funded health program (VicHealth) who worked in indigenous communities for many years observed:

> What I learned I guess is that you realise that why people get sick is a lot more than a germ. It's really the social and economic determinants of health . . . its whether someone has got a job, it's their educational levels and really, it's the amount of control they have over their own destiny . . . If people are told they're no good for long enough and it's repeated generation after generation, it profoundly affects them, no matter who they are. Discrimination causes ill health, there's no doubt about it. (Moodie 1999, p 7)

Based on this understanding, the HRSCFCA (2000) has recommended a holistic approach to health improvement that covers the areas of public health, environmental resources, education and training, economic factors, representation, participation and reconciliation.

Many indigenous people live in remote communities with few facilities. Their housing is inadequate, as is access to water, power, sanitation, nutritious food at a reasonable price, medical facilities and work. The public health measures that will be addressed in this holistic approach to indigenous health include provision of safe water (Bursill 2002), sanitation, better nutrition and supply of fresh fruits and vegetables (O'Dea 2000; Rowley et al 2000), housing and infrastructure, increased community control of medical services, community appropriate support to deal with issues of substance abuse and domestic violence (HRSCFCA 2000).

The medical interventions specifically mentioned by the HRSCFCA include:

- monitoring for ear disease on a regular basis from birth, and hearing tests for all indigenous children by three years of age.
- improving nutrition and community support for pregnant women and mothers.
- pooling of community funds provided by the Medical Benefits Scheme, the Pharmaceutical Benefits Scheme and other government funds to provide relevant hospital and medical services.
- programs to encourage medical practitioners to work in isolated communities.
- programs to encourage indigenous people to train in medical and related health professions.

(HRSCFA 2000).

In this comprehensive and thorough approach to improving standards of indigenous health, immunisation was not mentioned separately or specifically addressed. It was presumed to be appropriately included under general provision of medical services. In this matter the HRSCFA has placed immunisation in its proper perspective, as a useful medical component of a holistic approach to the health of a community. This shows an appreciation that:

> . . . health funding works best when accompanied by social changes that deliver more real opportunity, power and respect to indigenous communities. (Glover 1999, p 2)

The development of this policy demonstrates that it is possible for a nation to develop a holistic approach to health for its communities. Although there is a long way to go to bring indigenous health in line with that of the non-indigenous community, useful progress is being made (Australian Broadcasting Commission 2002, NHMRC 2000b, Video Education Australia 2000). The next step would be to use a similar approach to the health of the non-indigenous poor in Australia, for although their general health and life expectancy may not be as dramatically bad as that of the indigenous communities, they are certainly far from optimal.

15.7.2 IMMUNISATION FOR ABORIGINES AND TORRES STRAIT ISLANDERS

There has been a change of policy regarding the immunisation of indigenous people between the publication of the NHMRC Immunisation Handbooks in 1997 and 2000.

In the Immunisation Handbook (2000a) there is a separate section discussing the health situation and immunisation requirements of indigenous people. It points out that they "experience a much greater burden of infectious diseases than do other Australians" (p 68) and that only "some of these are vaccine preventable" (p 68). The immunisation schedule is now the same for indigenous children as for all other Australians. Previously it had differed, for example the MMR vaccine was administered at 9 months. The age has now been raised to 12 months, in line with the rest of the population.

The discussion of indigenous health by the NHMRC also includes information on race-specific traits of response to immunisation. Particularly, these include "suboptimal" (NHMRC 2000a, p 68) responses to the hepatitis B vaccines, shown in a small percentage of cases, and in general to OPV. It is noted that:

> This has also been observed in children in developing countries, where it has been attributed to a complex array of factors related to the vaccine, host and environment. (NHMRC 2000a, pp 68-69)

It is worth noting here the implications of the use of the term “suboptimal”. Embedded within this term is the notion of comparison with the responses of Caucasians. It arises from a very ethnocentric view of science. The responses to these vaccines may simply be different in ways that have not yet been quantified, and may or may not relate to immunity (see Sections 2.8 & 9.3.4). As antibody count has been shown to have little relationship to actual immunity (see Chapter 6) a lower antibody count in response to the vaccine may not be significant and need not be seen as ‘inferior’.

One positive development has been a reduction in the incidence of hepatitis A. Previously (the NHRMC does not specify when) it was “hyperendemic” (NHMRC 2000a, p 71) with up to 90% of indigenous children infected before 5 years of age, particularly in the Northern Territory. Improvements in living conditions, water supply and sanitation have led to an upward shift in the age of infection to about 12 years. This has brought it to an age where infection is more obvious, and therefore awareness of the extent of the problem has been raised and uptake of the offered vaccine has increased (NHMRC 2000a).

The NHMRC has shown an awareness of the need to provide

> . . . relevant and appropriate information for the parents of indigenous children and [a] need for high quality training for the service providers, in particular for indigenous health workers. (NHMRC 2000a, p 72)

This encompasses designing culturally appropriate methods of provision, such as outreach or home visit programs, to access both children and adults

> . . . innovative strategies will be necessary to reach those at high risk, such as the homeless and those with alcohol problems. (NHMRC 2000a, p 72)

In these regards the NHMRC deserves credit for responding in an appropriate manner to the particular requirements of Australia’s indigenous population, and

showing an appreciation of both genetic and cultural differences in response and uptake. In this regard, the immunisation program for Aboriginal and Torres Strait Islanders can take its place as part of a holistic approach to improving the quality of their health.

15.8 CONCLUSION

In many respects the situation in Australia with regards to immunisation is comparable with many international trends. Amongst industrialised nations, and particularly the English speaking ones, there is a broad similarity in government policies, problems with supply, medical practitioner performance and consumer complaints. In Australia's favour are a broad based and therefore relatively secure supply chain, an increasing respect for the particular needs of community groups such as the Aboriginal and Torres Strait Islanders, wider parameters for the reporting of adverse reactions and an appreciation of the benefits of holistic health policy.

CHAPTER 16

CONCLUSION

16.1 IMMUNOLOGY AND IMMUNISATION

As has been demonstrated in this thesis, at all levels of scientific knowledge and endeavour relating to the creation of vaccines there are complexities and uncertainties, and sometimes these are not acknowledged. The physical attributes and mechanisms of the immune system reported as facts in standard immunological texts are the subject of considerable conjecture and dispute. This includes the nature and function of cells and molecules that are central to current understandings of the way immunisation operates, with the result that vaccine design is often achieved through empirical means without the support of a clear theoretical basis for the procedures, or a clear understanding of the reasons for the results obtained.

It is a natural process for the theoretical framework of scientific disciplines to evolve over time, with cycles of stability interspersed by periods of turmoil and rapid change as new paradigms replace old ones. Over the last decade immunology has been experiencing such a change, with evidence of an increased dissatisfaction with the traditional view that the central function of the immune system is to discriminate self from nonself. A variety of new theories have been proposed, with the most significant being the danger model that sees the immune system as responding to unnatural cell death, and various perceptions of the immune system as a regulator of homeostasis. Although there is evidence that these new theories

are gaining some acceptance in a variety of areas of medical research, they have not yet become integrated into discussions on the theoretical basis for the development of vaccines. This is a matter for concern as they carry significant implications for vaccine design, in particular the need for vaccines to provide appropriate “danger” signals to stimulate the immune system.

The attenuated, killed or particulate nature of pathogens included in vaccines do not generally, on their own, provide sufficient stimulus or “danger” to provoke an adequate immune response. Vaccine designers therefore rely heavily on the use of various adjuvants to assist this process. These adjuvants are diverse in nature and little is understood about their mode of operation. Many new adjuvants are being trialled for human use, but all have significant limitations. Particular care needs to be taken in the evaluation and approval of those intended for use in neonates and infants.

The discussion of neonatal tolerance provides further support for the new theories in immunology. There is evidence that the current practice of administering large doses of antigen to infants to overcome the phenomenon of neonatal tolerance may be erroneous. This conclusion is based on *in vitro* studies that show that a low to moderate dose of antigen is more effective than a large one. This has been supported by the effectiveness of reduced dose vaccines in the field. The crucial factor is not the amount of antigen, but the way in which it is presented to the immune system. In other words there is not the need to flood the neonatal system with a large amount of “nonself”, but rather to present the antigen in such a manner that it is interpreted as a “danger” to be dealt with in such a way that a memory of that antigen persists.

However, there is a lack of understanding about the mechanisms of immunological memory. There is no consensus on how it is generated or maintained over time. There are also no clear parameters for measuring memory. This is because the current standard of measurement, antibody levels, is not an adequate or comprehensive measurement of immune response, and does not correlate strongly with protection from disease.

Despite increasingly detailed knowledge of the function of many aspects of the immune system, vaccine design remains largely empirically, rather than theoretically, driven. The increasing trend towards specialisation in science exacerbates this situation as few researchers demonstrate an appreciation of the function of the immune system in relationship with other biological systems and the body as a whole. As a result the discipline of immunology lacks a clear theoretical basis to support the design and creation of vaccines.

16.2 IMMUNISATION AND EFFICACY

There are significant areas of concern pertaining to the efficacy of various aspects of the administration of immunisation to individuals. This includes longer-term reactions, immunological and epidemiological studies of vaccine efficacy, and the complexities of supply.

Longer-term negative health outcomes, such as atopy or autoimmune diseases, as a result of immunisation are generally denied by the medical establishment and public health officials. However, current immunological theory and experimental evidence provide support for the potential for these conditions to occur as a result of immunisation. Current data collection methods do not provide the means for these issues to be adequately addressed. There is a lack of studies examining potential links between severe adverse reactions at the time of immunisation and

later health outcomes, and studies examining why some individuals experience particular adverse reactions and others do not. These represent fruitful areas of future research.

The issue of adverse reactions is linked to the whole area of vaccine efficacy. Both immunological and epidemiological studies have proven to be of limited use owing to limitations in study design, inadequacy of measurement parameters and confounding variables. In the case of immunological studies of vaccine efficacy a primary concern is that those indicators of immune response which can be easily and conveniently measured do not correlate well with protection from disease. Currently the measurement used is serum antibody levels, even though there is substantial evidence that this is inadequate. Further confounding factors include variations in individual and racial/ethnic immune responses, pathogen variations, vaccine variations and non-comparability of assay results between different laboratories.

Epidemiological studies have a similar range of problems including poor study design, inability to usefully compare studies owing to limitations in collecting and reporting data, sample size, selection and follow up. Other confounding factors include inadequate reporting of disease case definition, variations in method of vaccine administration, background incidence of disease and variations in currently circulating strains of pathogens. A further widespread limitation of both immunological and epidemiological studies of vaccine efficacy is the lack of data collected on the socio-economic conditions and health status of research participants. This is an area where more comprehensive data are relatively easy to collect and may offer valuable insights into the reasons for various findings on vaccine efficacy and nature and prevalence of adverse reactions.

An overview was given of the practical problems involved in supplying vaccines to the public. Each area examined, including quality and quantity of supply, transport, storage and provision was characterised by its own set of issues and difficulties. In each of these areas similar problems are faced by both industrialised and developing nations, and the end result is compromise in the quality of product delivered to the public, with consequent risk.

16.3 IMMUNISATION AND SOCIAL POLICY

Immunisation is a component of public health policy, and the way in which its position within this policy is regarded has implications for public health outcomes at local, national and international levels. There is evidence of the influence of broad socio-economic factors upon population health. This includes the roles played by social status and stress in the aetiology of infectious disease within communities. The determinants of health are broader than access to health care, and include factors as diverse as education, equity of income, economic and social security and cultural and policy support for women and children. Neo-classical economic theories have influenced the recognised health indicators of both developing and industrialised nations. These economic policies such as privatisation, financial deregulation and user-pays schemes have had profound negative health outcomes for many nations. While millions of people in both industrialised and developing nations lack access to adequate nutrition, safe water and sanitation, immunisation as a preventative measure for infectious disease remains at the level of a useful bandaid approach. Lasting improvements in the health status of populations will only come about when the underlying economic and social causes are addressed. Much can be gained from moving away from a reductionist perspective that views immunisation as the main tool for the prevention of infectious disease (as it only covers a few diseases anyway) and towards a holistic and wide ranging approach to public health aimed at increasing population health resilience. This is suggestion

is not meant to detract from the useful role that is played by immunisation, but rather seeks to complement it with a greater focus on the wider causes of disease.

Currently these problems are being exacerbated rather than alleviated by the approach of international immunisation programs such as GAVI. The increasing involvement of multinational corporations in the development of complex and expensive combination vaccines is increasing social inequity at both a national and international level. While the expenditure and publicity surrounding immunisation provides the appearance that health inequalities are being addressed, more important, although less lucrative aspects of public health are neglected.

There are both epistemological and ethical aspects to this situation. Scientists may filter the collection of relevant data with the effect of maintaining the current dominant understanding of the role of immunisation. Evidence of the adverse effects of immunisation from both the lay and scientific community are down-played in public health debate.

The utilitarian argument is the main ethical position used to justify the emphasis on maintaining herd immunity via universal immunisation in preference to the rights of the individual. This argument is appealing when immunisation is treated in isolation, but when a broader perspective on public health and disease prevention is employed to shift the parameters of the underlying assumptions, the use of the utilitarian argument to justify coercive immunisation policies becomes less convincing. In this way coercive immunisation policies arise in a deregulated economy in response to the government needing to appear involved in the provision of public health, even if the programs and their methods of evaluation are inadequate. This may allow the underlying, and more complex causal factors of disease to remain unaddressed. In contrast, a deontological position that values

the rights of the individual provides the philosophical basis for public health policy. This position has the benefit of being in accordance with the growing emphasis on informed consent and current findings on long-term individual and national health outcomes.

Australian policy with respect to immunisation is generally viewed positively in this thesis. Although the common problems with vaccine supply, storage and service provision are alive and well, there is an awareness of these problems and efforts are regularly made to address them. Notifying the Department of Health about one's choice to immunise or not is compulsory. However immunisation itself is not compulsory, although highly advocated. Ethical concerns have been raised regarding the financial incentive scheme implemented to encourage medical practitioners to immunise and report to the ACIR, but this incentive scheme does allow for some flexibility of choice on the part of the consumer. Recent policy changes are in line with encouraging increased reporting of adverse events and greater consumer involvement in decision making. The comprehensive public health policy aimed at improving the health status of the Aboriginal and Torres Strait Islander populations shows an appreciation of the importance of broader social and economic issues as determinants of health.

16.4 CONCLUSION

Paediatric immunisation is a public health measure that crosses the boundaries of many disciplines including immunology, epidemiology, public health policy and administration, medical practice, ethics, economics, politics and finance. In all areas there are areas of dispute, problems and complexities.

The current state of knowledge and theory in immunology is unclear with respect to the mechanisms of operation of vaccines and parameters with which to measure

their efficacy. Given this state of uncertainty this thesis suggests that there does not currently exist sufficient epistemological certainty to justify compulsion to immunise in public health policy.

Currently there exists considerable scope for improved data collection methods on broader socio-economic and health status influences on the efficacy of vaccines. There is also a useful role for studies into factors that cause and exacerbate adverse reactions, and an examination of a potential link between short-term adverse reactions and longer-term negative health outcomes. There are many technical and administrative challenges to be met in the consistent provision of a quality product to the consuming public, both in developing and industrialised nations.

Currently available paediatric vaccines target relatively few infectious diseases. Given the high cost and long periods of time required for research, development and licensing of each new vaccine the overall efficacy of this approach to this method of preventing infectious disease deserves considered debate. Substantial evidence exists to demonstrate the profound health effects of broad-based economic and social factors on the health status of populations in general, including the incidence of infectious diseases. There still exists considerable scope for improving the provision of basic health needs such as nutrition, safe water and sanitation in the populations of both developing and industrialised nations. Further to this are the roles played by income inequality, economic security, social cohesion and personal self-esteem in the health of populations in general. Where these factors are inadequate and the population is under stress, this stress will manifest in negative health outcomes, and focusing on preventing outbreaks of infectious disease then becomes merely a bandaid measure, albeit a useful one, leaving primary causes unaddressed.

Currently immunisation is most productively viewed as a useful component in a broad-ranging public health policy, but it is certainly not the only preventative measure for infectious disease, or necessarily the most effective. Given the trend towards more expensive combination vaccines and the complexities of adding to an already overcrowded paediatric immunisation schedule, immunisation as a preventative measure for infectious disease may eventually decline in cost effectiveness. When this occurs, the medical establishment, industry and governments may be encouraged to adopt a more holistic approach to disease prevention and a broad-based promotion of public health resilience.

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